# CERTAIN 1,3-DISUBSTITUTED ISOQUINOLINE DERIVATIVES

This application is a divisional of co-pending Application No. 09/852,850, filed May 11, 2001, which is a divisional of 09/509,778, filed on March 31, 2000 (now USP 6,340,759B1) and for which priority is claimed under 35 U.S.C. § 120. Application No. 09/509,778 is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP98/04465 filed on October 2, 1998. The entire contents of each of the above-identified applications is hereby incorporated by reference. This application also claims priority under 35 U.S.C. § 119 to Application No. 9-284290 filed in Japan on October 2, 1997.

## Field of the Invention

The present invention relates to a clinically useful medicament having a serotonin antagonism, in particular, that for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

## Background of the Invention

Myotonia, which seriously restrains daily life, is induced by any of a number of factors or a combination thereof, for example, cervico-omo-brachial syndromes accompanying stiffness or pain in the neck, shoulder, arm, lumbar and dorsal skeletal muscles due to abnormal posture, fatigue, changes in the backbone with ageing etc., shoulder periarthritis accompanying inflammation in the tissues constituting the shoulder joint due to changes in the shoulder joint caused by trauma, etc., and spastic

paralysis wherein accelerated limb muscle tonus hinders voluntary movements.

In particular, spastic paralysis is a disease which accompanies limb muscle tonus, stiffening, walking difficulty, etc. and thus seriously restrains daily life.

Prior Art

It has been a practice to treat these diseases mainly with the use of medicaments. At the present stage, central muscle relaxants or peripheral muscle relaxants are administered to patients with these diseases.

Particular examples of used central muscle relaxants include Tolperisone hydrochloride, Baclofen, Tizanidine hydrochloride, Chlorzoxazone and Diazepam.

On the other hand, particular examples of used peripheral muscle relaxants include suxamethonium chloride, Pancuronium bromide and dantrolene sodium.

Central muscle relaxants act selectively on the central nervous system so as to relax muscles. Therefore, it is expected that those action on the upper center would exhibit a more potent muscle relaxant effect. However, there arise at the same time some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness and atony. Namely, there has been known hitherto no medicament capable of achieving well-balanced principal action and side effects.

Diazepam, which is inherently a minor tranquilizer, is efficacious against diseases accompanying mental symptoms such as anxiety, tension

and depression. However, its effect is too potent to merely ameliorate myotonia. With the use of diazepam, therefore, spastic paralysis can be relieved but there arise some problems such as dizziness.

On the other hand, suxamethonium chloride and Pancuronium bromide which are peripheral muscle relaxants are marketed exclusively as injections, which makes the chronic administration thereof difficult.

Dantrolene sodium is processed into injections and preparations for oral use and has a relatively potent muscle relaxant effect. However, it suffers from problems of having only a low margin of safety and frequently inducing muscular atony. Accordingly, it is difficult for those other than medical specialists to administer this medicine.

As discussed above, there has been known hitherto no medicaments for treating and ameliorating myotonia in spastic paralysis etc., which is clinically useful and has a high safety.

## Disclosure of the Invention

Under these circumstances, the present inventors have conducted extensive studies to develop medicaments for treating, ameliorating and preventing spastic paralysis or central muscle relaxants which have a potent effect of ameliorating myotonia while sustaining a high safety and newly paid their attention to compounds having a serotonin antagonism. As a result, they have successfully found that a novel condensed pyridine compound represented by the following formula or a pharmacologically acceptable salt thereof has an excellent central muscle relaxant effect and a high safety and thus makes it possible to solve the above problems, thus completing the present invention.

Accordingly, the present invention aims at providing clinically useful novel medicaments which have well-balanced principal action and side effects and make it possible to overcome the problem encountering in the prior art that those acting on the upper center would exhibit a more potent muscle relaxant effect but at the same time suffer from some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness and weakness.

Because of the anti-serotonin effect, it is expected that the condensed pyridine compound of the present invention is moreover usable in preventing, treating and ameliorating depression, emotional disorders, schizophrenia, sleep disturbance, anxiety, spinal cord injury, thrombosis, hypertension, brain circulatory disturbances, peripheral circulatory disturbances, drug addiction, etc.

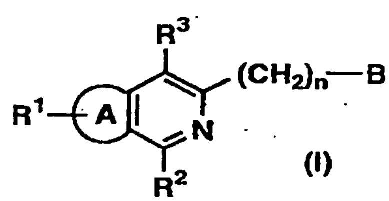
In addition to the condensed pyridine compound, the present invention provides medicinal composition which comprises a pharmaceutically effective dose of the condensed pyridine compound, its pharmaceutically acceptable salt or hydrates thereof and pharmaceutically acceptable carriers. Further, it provides an agent for treating, ameliorating or preventing diseases against which serotonin antagonism is efficacious, an agent for treating, ameliorating or preventing spastic paralysis and a muscle relaxant, which comprise the above-mentioned active ingredient.

Further, it provides a treating, ameliorating or

prophylactic agent comprising the above-mentioned effective ingredient for diseases for which the serotonin antagonism is efficacious or , a therapeutic, ameliorating and prophylactic agents of spastic paralysis and a muscle relaxation agent.

Furthermore, it provides a method for treating diseases against which the serotonin antagonism is efficacious or spastic paralysis, or ameliorating myotonia, which comprising the step of administering a pharmacologically effective dose of the condensed pyridine compound, its pharmacologically acceptable salt or hydrates thereof to a patient. Additionally, it provides the use of the effective ingredient for producing the above-mentioned medicaments.

Herein, the condensed pyridine compound (I) of the present invention is represented by the following formula:

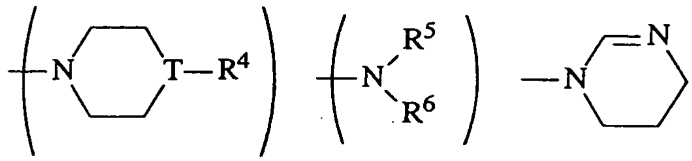


(I)

wherein, ring A represents benzene ring, pyridine ring, thiophene ring or furan ring;

$R^1$ represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxyl group;

$R^2$ represents 4-morpholinyl group, 1-imidazolyl group, 1-lower alkyl homopiperazin-4-yl group or any one selected from the groups represented by the following formulae:



(wherein, T represents nitrogen atom or methine group;

$R^3$ represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxyl group;

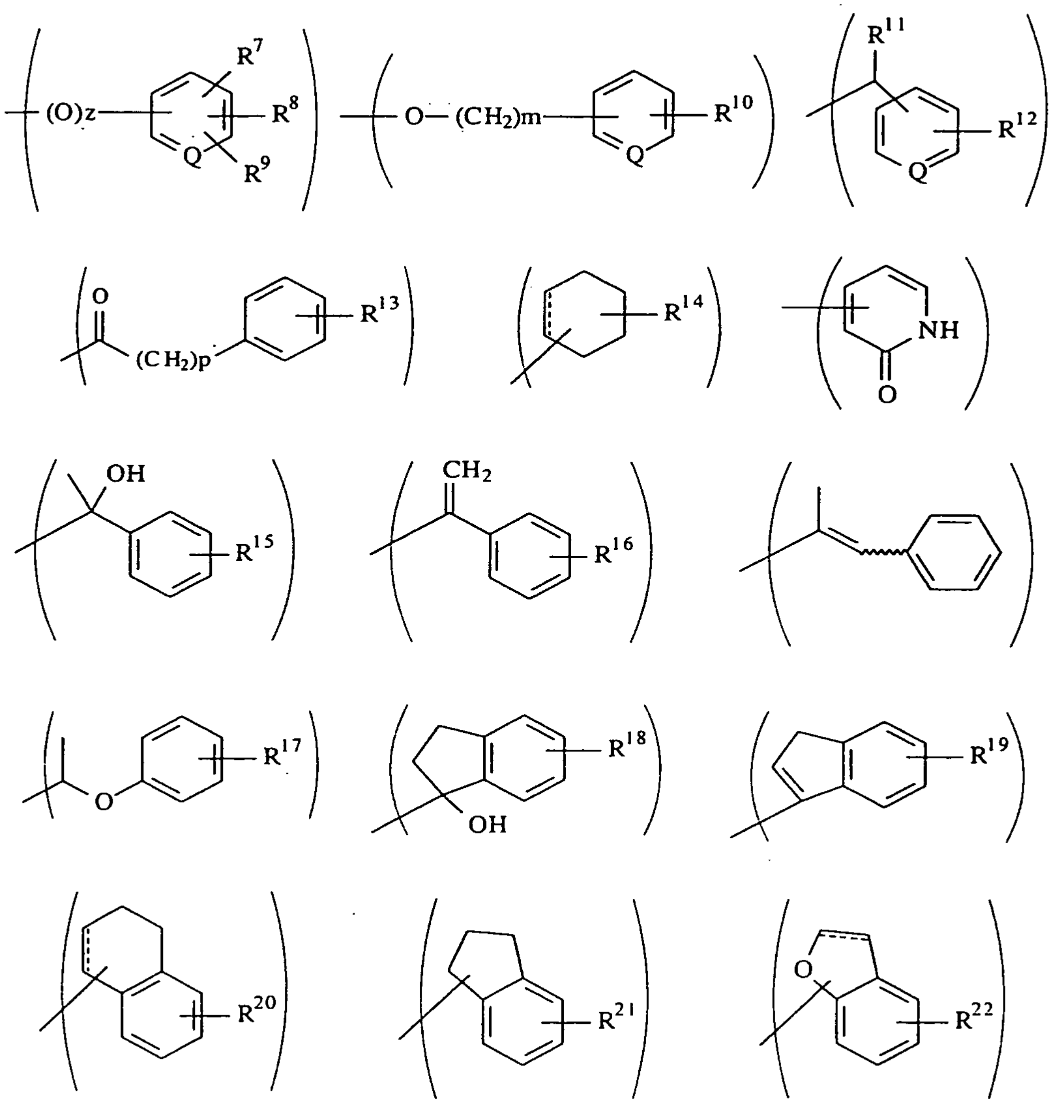
$R^4$ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group, a halogenated lower alkyl group, a lower cycloalkyl group, an aryl group, an aralkyl group, 1-piperidyl group, an alkenyl group, a cyano lower alkyl group, a carbamoyl lower alkyl group, a lower acyl group, an aromatic acyl group, a lower alkoxyl carbonyl group, an aryloxycarbonyl group or an aralkyloxycarbonyl group;

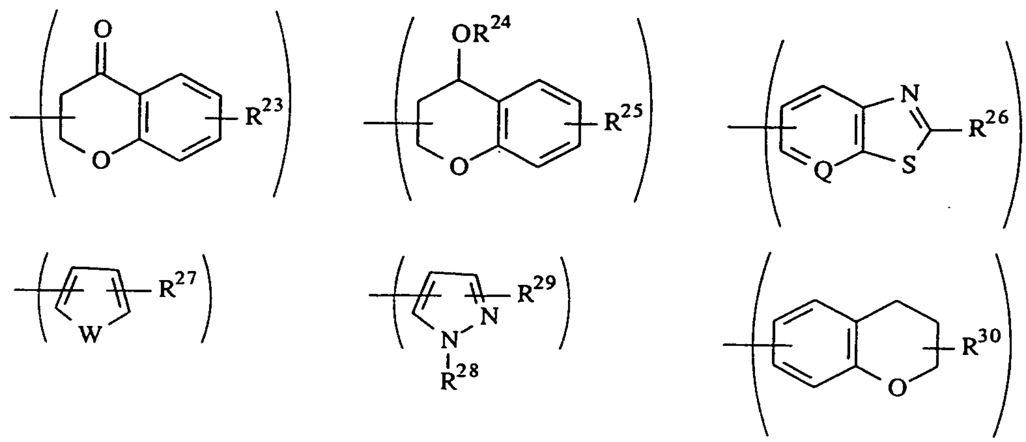
$R^5$ and $R^6$ are the same as or different from each other and each represents hydrogen atom, a lower alkyl group, a di lower alkyl aminoalkyl group, an optionally substituted heteroaryl lower alkyl group);

n represents 0 or an integer of 1 to 6; and

B represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyloxy group, an aryl(hydroxy)alkyl group, an aromatic acyl amino group, an arylsulfonylamino group, a lower alkoxyl arylsulfonylamino group, a hydroxy lower alkoxyl styryl group, a lower alkoxyl aryloxy group, 4-phenylpiperidin-1-yl group, 4-pyridylpiperidin-1-yl group, an optionally substituted arylalkenyl group, an optionally substituted

arylalkynyl group, an optionally substituted heteroarylalkenyl group, an optionally substituted heteroarylalkynyl group, an aromatic acyl alkynyl group, an optionally N-substituted amino lower alkyl group, an optionally substituted arylamino group, an optionally substituted aralkylamino group or any one selected from the groups represented by the following formulae:





(wherein z represents 0 or 1;

Q represents nitrogen atom or methine group;

$R^7$, $R^8$ and $R^9$ are the same as or different from each other and each represents hydrogen atom, halogen atom, hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxyl group, a lower thioalkoxyl group, a hydroxy lower thioalkoxyl group, an arylthio group, a heteroarylthio group, a heteroaryl(hydroxy)alkyl group, a halogenated lower alkyl group, a hydroxy lower alkyl group, a dihydroxy lower alkyl group, a halogenated (hydroxy) lower alkyl group, a hydroxyalkenyl group, a hydroxyalkynyl group, a hydroxy lower cycloalkenyl group, a lower alkoxy(hydroxy)alkyl group, a lower alkoxy(hydroxy)alkoxy group, a lower alkoxyalkyl group, a lower alkoxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkylsulfonylalkoxy group, a hydroxy lower alkoxy group, a dihydroxy lower alkoxy group, a hydroxy lower alkylalkoxy group, a hydroxyimino lower alkyl group, a lower cycloalkyl (hydroxy) alkyl group, an aralkyl group, a hydroxyaralkyl group, cyano group, a cyano lower alkyl group, amide group (carbamoyl group),

an N-lower alkylamide group, an N-lower cycloalkylamide group, an N,N-di lower alkylamide group, an N-hydroxy lower alkylamide group, an N-hydroxy lower alkyl-N-lower alkylamide group, an N-arylamide group, cyclic aminocarbonyl group, carbamoyl group, an N-lower alkyl carbamoyl group, an N,N-di lower alkyl carbamoyl group, aminosulfonyl group, cyclic aminosulfonyl group, an N-lower alkylaminosulfonyl group, an N-lower cycloalkylaminosulfonyl group, an N,N-di lower alkylaminosulfonyl group, an N-hydroxy lower alkylaminosulfonyl group, an N-lower alkoxyalkylaminosulfonyl group, an N-halogenated lower alkylsulfonyl group, pyrrolidinylsulfonyl group, a lower alkylsulfonylaminoalkyl group, an N-lower alkylaminosulfonylalkyl group, an N,N-di lower alkylaminosulfonylalkyl group, a lower acyl group, a lower acylalkyl group, a lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, a hydroxy lower alkyltetrahydropyranyl group, a lower acylaminoalkyl group, (thiazol-2-yl)hydroxymethyl group, di(thiazol-2-yl)hydroxymethyl group, a lower alkylsulfonyl group, a lower alkoxyalkylsulfonyl group, a hydroxy lower alkylsulfonyl group, a lower alkylsulfonylalkyl group, an N-lower alkylamidealkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroaryl lower alkyl group, a heteroaryl lower alkoxy group, a heteroarylsulfonyl group, 4-morpholinylsulfonyl group, 4-oxythiomorpholinylsulfonyl group, 4-dioxythiomorpholinylsulfonyl group, 4-

morpholinylsulfonyl group, a hydroxy lower cycloalkyl group, a hydroxy lower cycloalkyloxy group, a hydroxycycloalkenyl group, a halogenatedhydroxy lower alkyl group, 4-hydroxypiperidyl group, a 4-lower alkoxypiperidyl group, an ω,ω-lower alkylenedioxyalkyl group, an ω,ω-lower alkylenedioxyalkoxy group, a lower cycloalkylhydroxymethyl group, an aryloxy group, an arylaminosulfonyl group, amino group, a lower alkylamino group, a di lower alkylamino group, a hydroxy lower alkylamino group, a lower acylamino group, a hydroxy lower acylamino group, a lower alkylsulfonylamino group, a pyridyl lower alkoxy group, a lower alkylpyridylalkoxy group, a lower alkoxyhydroxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkylsulfonylalkoxy group, an N-lower alkylcarbamoyl group, an N,N-di lower alkylcarbamoyl group, an N-hydroxy lower alkylcarbamoyl group, an N-hydroxy lower alkyl-N-lower alkylcarbamoyl group, a halogenated lower alkoxy group, a cyano lower alkoxy group, a hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, an amino lower alkoxy group, an N-lower alkyl aminoalkoxy group, an N,N-di lower alkylaminoalkoxy group, a lower acylalkoxy group, a lower acylaminoalkoxy group, a (1,3-dioxolanyl) lower alkyl group, a (1,3-dioxolanyl) lower alkoxyl group, an amide lower alkoxyl group, a 4-(hydroxyalkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, a 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, an imidazolyl lower alkoxyl group, succinimide group or

2-oxazolidon-3-yl group;

furthermore, $R^7$ represents hydrogen atom, while $R^8$ and $R^9$ form cyclopentanone ring, hydroxycyclopentane ring, a hydroxyalkylcyclopentane ring, cyclohexanone ring, hydroxycyclohexane ring, a hydroxyalkylcyclohexane ring, 2-hydroxymethyl-2-methylcyclopentanone ring, 1,2-ethylenedioxy ring or methylenedioxy ring;

m or p represents 0 or an integer of 1 to 6;

$R^{10}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$, $R^{21}$, $R^{22}$, $R^{23}$, $R^{25}$, $R^{27}$ and $R^{29}$ independently represent hydrogen atom, halogen atom, hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group, a hydroxy lower alkoxy group or tetrahydropyranyl group;

$R^{11}$ represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group or a lower alkoxy group;

$R^{24}$ represents hydrogen atom or a lower alkyl group;

$R^{26}$ represents hydrogen atom or a hydroxy lower alkyl group;

$R^{28}$ represents hydrogen atom or a lower alkyl group;

$R^{30}$ represents hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group or a hydroxy lower alkoxy group;

W represents sulfur atom or oxygen atom;

the bond represented by the following formula:

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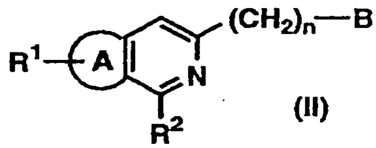
represents a single or double bond; and

the bond represented by the following formula:

represents trans or cis bond.).

Among these condensed pyridine compounds, the condensed pyridine compound (II) represented by the following formula is more preferable:

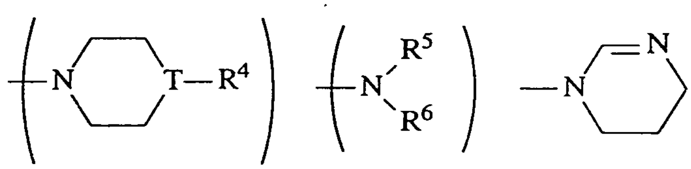


(II)

wherein, ring A represents benzene ring, thiophene ring or furan ring;

$R^1$ represents hydrogen atom, halogen atom, a lower alkyl group or a lower alkoxy group;

$R^2$ represents 4-morpholinyl group, 1-imidazolyl group, a 1-lower alkylhomopiperazin-4-yl group or any one selected from the groups represented by the following formulae:



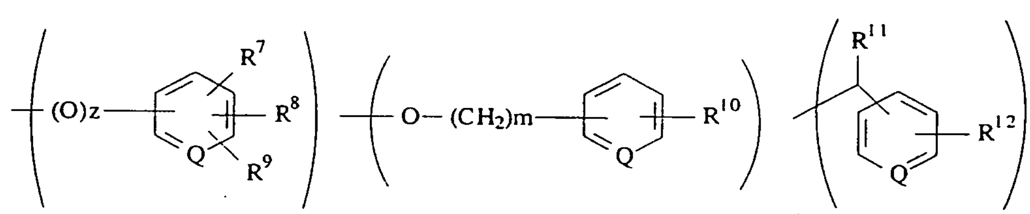
(wherein, T represents nitrogen atom or methine group;

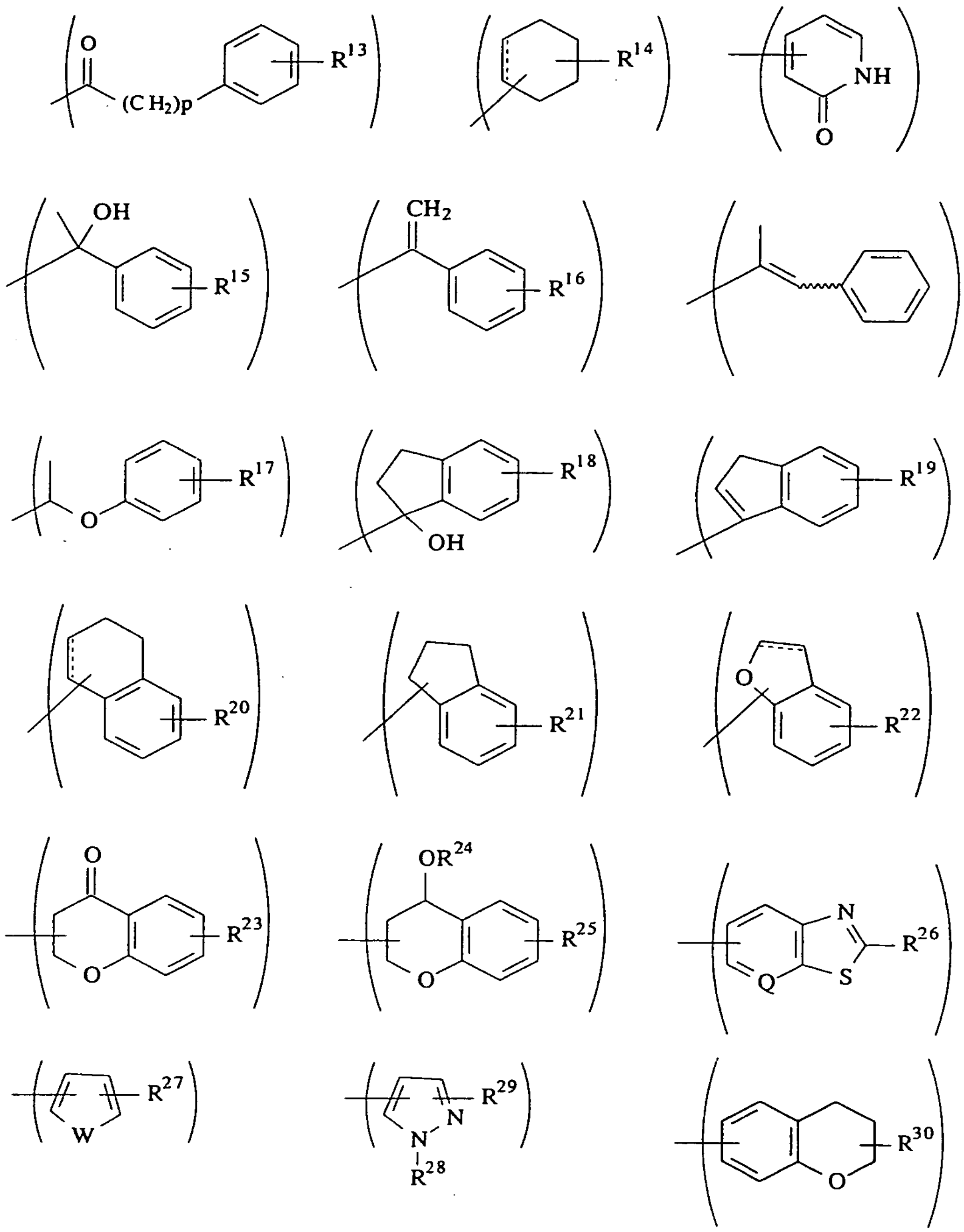
$R^4$ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group, a halogenated lower alkyl group, a lower cycloalkyl group, an aryl group, an aralkyl group, 1-piperidyl group, an alkenyl group, a cyano lower alkyl group, a carbamoyl lower alkyl group, a lower acyl group, an aromatic acyl group, a lower alkoxy carbonyl group, an aryloxycarbonyl group or an aralkyloxycarbonyl group; and

$R^5$ and $R^6$ are the same as or different from each other and each represents hydrogen atom, a lower alkyl group, a di lower alkylaminoalkyl group, an optionally substituted heteroaryl lower alkyl group.);

n represents 0 or an integer of 1 to 6; and

B represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyloxy group, an aryl(hydroxy)alkyl group, an aromaticacylamino group, an arylsulfonylamino group, a lower alkoxyarylsulfonylamino group, a hydroxy lower alkoxystyryl group, a lower alkoxyaryloxy group, 4-phenylpiperidin-1-yl group, 4-pyridylpiperidin-1-yl group, an optionally substituted arylalkenyl group, an optionally substituted arylalkynyl group, an optionally substituted heteroarylalkenyl group, an optionally substituted heteroarylalkynyl group, an aromaticacylalkynyl group, an optionally N-substituted amino lower alkyl group, an optionally substituted arylamino group, an optionally substituted aralkylamino group or any one selected from the groups represented by the following formulae:





(wherein, z represents 0 or 1;

Q represents nitrogen atom or methine group;

$R^7$, $R^8$ and $R^9$ are the same as or different from each other and each represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group,

a lower alkoxy group, a lower thioalkoxy group, a hydroxy lower thioalkoxy group, an arylthio group, a heteroarylthio group, a heteroaryl(hydroxy)alkyl group, a halogenated lower alkyl group, a hydroxy lower alkyl group, a dihydroxy lower alkyl group, a halogenated(hydroxy) lower alkyl group, a hydroxyalkenyl group, a hydroxyalkynyl group, a hydroxy lower cycloalkenyl group, a lower alkoxy(hydroxy)alkyl group, a lower alkoxy(hydroxy)alkoxy group, a lower alkoxyalkyl group, a lower alkoxyalkoxy group, a lower thioalkoxyalkoxy group, a lower alkyl sulfonylalkoxy group, a hydroxy lower alkoxy group, a dihydroxy lower alkoxy group, a hydroxy lower alkylalkoxy group, a hydroxyimino lower alkyl group, a lower cycloalkyl (hydroxy)alkyl group, an aralkyl group, a hydroxyaralkyl group, cyano group, a cyano lower alkyl group, amide group (carbamoyl group), an N-lower alkyl amide group, an N-lower cycloalkyl amide group, an N,N-di lower alkyl amide group, an N-hydroxy lower alkyl amide group, an N-hydroxy lower alkyl-N-lower alkyl amide group, an N-arylamide group, a cyclic amino carbonyl group, carbamoyl group, an N-lower alkyl carbamoyl group, an N,N-di-lower alkyl carbamoyl group, aminosulfonyl group, a cyclic amino sulfonyl group, an N-lower alkyl aminosulfonyl group, an N-lower cycloalkylaminosulfonyl group, an N,N-di lower alkyl aminosulfonyl group, an N-hydroxy lower alkylaminosulfonyl group, an N-lower alkoxyalkylaminosulfonyl group, an N-halogenated lower alkylsulfonyl group, pyrrolidinylsulfonyl group, a lower alkylsulfonylaminoalkyl group, an N-lower

alkylaminosulfonylalkyl group, an N,N-di lower alkylaminosulfonylalkyl group, a lower acyl group, a lower acylalkyl group, a lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, a hydroxy lower alkyltetrahydropyranyl group, a lower acylaminoalkyl group, (thiazol-2-yl)hydroxymethyl group, di(thiazol-2-yl)hydroxymethyl group, a lower alkylsulfonyl group, a lower alkoxyalkylsulfonyl group, a hydroxy lower alkyl sulfonyl group, a lower alkyl sulfonylalkyl group, an N-lower alkyl amidealkyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroaryl lower alkyl group, a heteroaryl lower alkoxy group, a heteroarylsulfonyl group, 4-morpholinylsulfonyl group, 4-oxythiomorpholinylsulfonyl group, 4-dioxythiomorpholinylsulfonyl group, 4-morpholinylsulfonyl group, a hydroxy lower cycloalkyl group, a hydroxy lower cycloalkyloxy group, a hydroxycycloalkenyl group, a halogenated hydroxy lower alkyl group, 4-hydroxypiperidyl group, a 4-lower alkoxy piperidyl group, an ω,ω-lower alkylene dioxyalkyl group, an ω,ω-lower alkylene dioxyalkoxy group, a lower cycloalkyl hydroxymethyl group, an aryloxy group, an arylaminosulfonyl group, amino group, a lower alkylamino group, a di lower alkylamino group, a hydroxy lower alkylamino group, a lower acylamino group, a hydroxy lower acylamino group, a lower alkylsulfonylamino group, a pyridyl lower alkoxy group, a lower alkylpyridylalkoxy group, a lower alkoxyhydroxyalkoxy group, a lower thioalkoxyalkoxy group, a

lower alkylsulfonylalkoxy group, an N-lower alkylcarbamoyl group, an N,N-di lower alkylcarbamoyl group, an N-hydroxy lower alkylcarbamoyl group, an N-hydroxy lower alkyl-N-lower alkylcarbamoyl group, a halogenated lower alkoxy group, a cyano lower alkoxy group, a hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, an amino lower alkoxy group, an N-lower alkyl aminoalkoxy group, an N,N-di lower alkylaminoalkoxy group, a lower acylalkoxy group, a lower acylaminoalkoxy group, a (1,3-dioxolanyl) lower alkyl group, a (1,3-dioxolanyl) lower alkoxy group, an amide lower alkoxy group, a 4-(hydroxyalkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, a 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, an imidazolyl lower alkoxy group, succinimide group or 2-oxazolidon-3-yl group;

furthermore, $R^7$ represents hydrogen atom, while $R^8$ and $R^9$ may form cyclopentanone ring, hydroxycyclopentane ring, a hydroxyalkylcyclopentane ring, cyclohexanone ring, hydroxycyclohexane ring, a hydroxyalkylcyclohexane ring, 2-hydroxymethyl-2-methylcyclopentanone ring, 1,2-ethylenedioxy ring or methylenedioxy ring;

m or p represents 0 or an integer of 1 to 6;

$R^{10}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$, $R^{21}$, $R^{22}$, $R^{23}$, $R^{25}$, $R^{27}$ and $R^{29}$ independently represent hydrogen atom, halogen atom, hydroxy group, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group, a hydroxy lower alkoxy group or

tetrahydropyranyl group;

the concrete examples of the heteroaryl group include 4-morpholinyl group, 2,6-dimethyl-4-morpholinyl group, 4-thiomorpholinyl group, 4-oxythiomorpholinyl group, 4-dioxythiomorpholinyl group, 1,3-dioxanyl group, 1,4-dioxanyl group, tetrahydrofuranyl group, dihydropyranyl group, 4,4-ethylenedioxypiperidin-1-yl group, 4-hydroxypiperidin-1-yl group, 4-methoxypiperidin-1-yl group, 4-acetylpiperazin-1-yl group, a 4-hydroxy lower alkyl piperidin-1-yl group and the like;

the concrete examples of the heteroaryl lower alkyl group include 4-morpholinylmethyl group, 4-thiomorpholinylmethyl group, a (tetrahydropyran-4-yl) lower alkyl group, pyridylmethyl group and the like;

$R^{11}$ represents hydrogen atom, halogen atom, hydroxy group, a lower alkyl group or a lower alkoxy group;

$R^{24}$ represents hydrogen atom or a lower alkyl group;

$R^{26}$ represents hydrogen atom or a hydroxy lower alkyl group;

$R^{28}$ represents hydrogen atom or a lower alkyl group;

$R^{30}$ represents hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy lower alkyl group or a hydroxy lower alkoxy group;

W represents sulfur atom or oxygen atom;

the bond represented by the following formula:

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represents a single or double bond; and

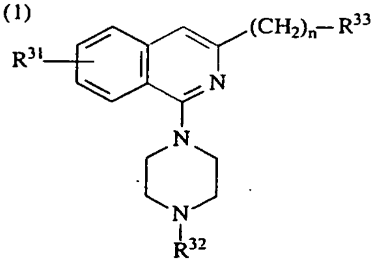
the bond represented by the following formula:



represents trans or cis bond.).

More specifically, the condensed pyridine compound of the present invention preferably include the condensed pyridine compounds represented by the following formulae:

(1)

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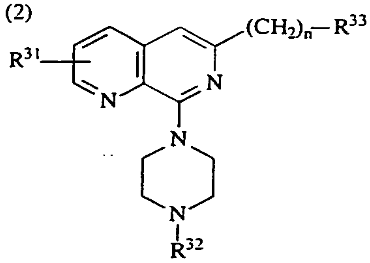


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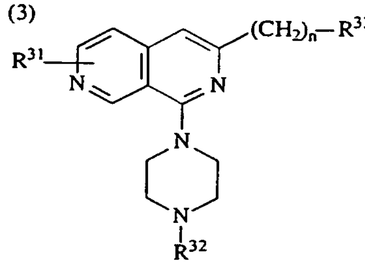


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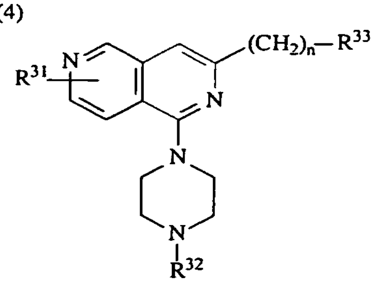


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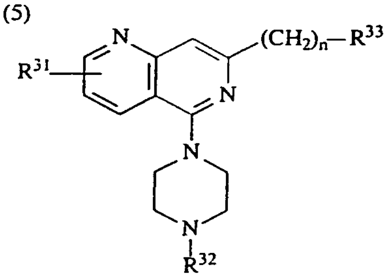


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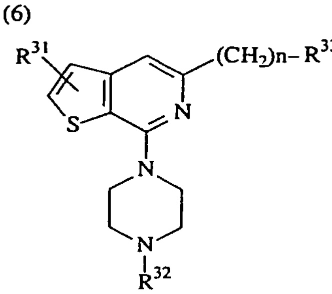


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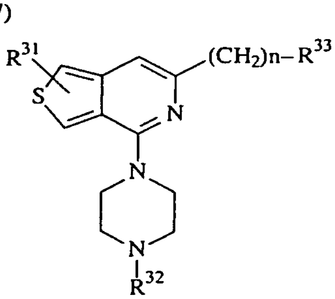


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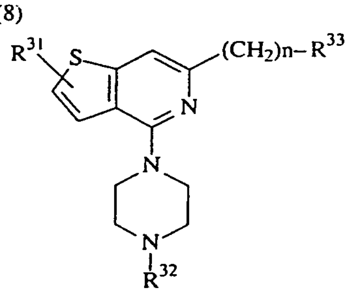


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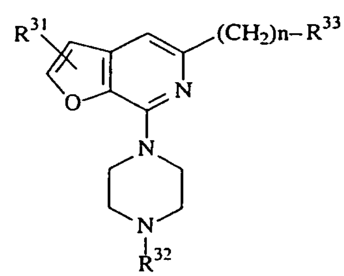


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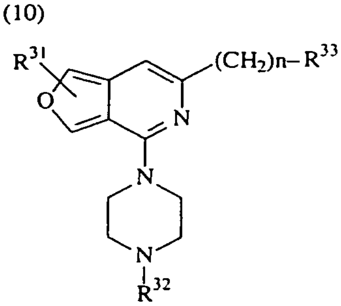


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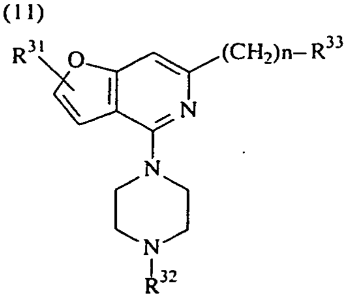


wherein, $R^{31}$ has the same meaning as that of the above $R^1$, $R^{32}$ has the same meaning as that of the above $R^2$ and $R^{33}$ has the same meaning as that of the above B, respectively.

More specifically, the condensed pyridine compound of the present invention preferably includes the following ones:

(1) 3-(4-benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(2) 1-(1-methylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(3) 1-(1-methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(4) 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethylphenyl)isoquinoline,

(5) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-fluoropropyl)phenyl]isoquinoline,

(6) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxyphenyl)isoquinoline,

(7) 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline,

(8) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxyphenyl)isoquinoline,

(9) 1-(4-ethylpiperazin-1-yl)-3-(3-methoxyphenyl)isoquinoline,

(10) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(11) 3-(2,3-dimethoxyphenyl)-1-(4-ethylpiperazin-1-

yl)isoquinoline,

(12) 3-(2,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(13) 3-(2,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(14) 3-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(15) 3-(3,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(16) 1-(4-ethylpiperazin-1-yl)-3-(2,4,5-trimethoxyphenyl)isoquinoline,

(17) 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline,

(18) 3-[2-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(19) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline,

(20) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline,

(21) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxybutyl)phenyl]isoquinoline,

(22) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline,

(23) 3-[4-(4-hydroxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(24) 3-[4-(1,3-dihydroxypropyl)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(25) 3-[4-(1,3-dihydroxy-3-methylbutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(26) 3-[4-(3-hydroxy-1-methoxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(27) 1-(1-ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline,

(28) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline,

(29) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline,

(30) 3-[3-chloro-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(31) 3-[3-carboxamide-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(32) 3-[3-cyano-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(33) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline,

(34) 3-[3-(3-hydroxypropyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(35) 3-[3-(4-hydroxybutyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(36) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(37) 3-[3,4-(2-dihydroxyethoxy)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(38) 3-[3,5-(2-dihydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(39) 3-[3-chloro-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(40) 3-[3-methyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(41) 3-[3-isopropyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(42) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline,

(43) 3-[3,4-(2-dimethoxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(44) 3-[4-(2-hydroxyethoxy)methylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(45) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline,

(46) 3-(3,4-methylenedioxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(47) 1-(1-ethylpiperazin-4-yl)-3-(4-acetonyloxyphenyl)isoquinoline,

(48) 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(49) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-dimethylaminoethoxy)phenyl]isoquinoline,

(50) 3-[4-(3-acetamidepropoxy)phenyl]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(51) 3-(4-cyanomethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(52) 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(53) 3-[4-(3-cyanopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(54) 3-[4-(3-methylthiopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(55) 3-[4-(3-methylsulfonpropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(56) 3-{4-[2-(1-imidazonyl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(57) 3-{4-[3-(4-pyridyl)propoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(58) 3-{4-[2-(2-methylpyridin-5-yl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(59) 1-(1-ethylpiperazin-4-yl)-3-[4-(N-ethylcarbamyl)phenyl]isoquinoline,

(60) (Z)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline,

(61) (E)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline,

(62) 3-(4-cyanophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(63) 1-(4-ethylpiperazin-1-yl)-3-(4-N-

propylaminocarbonylphenyl)isoquinoline,

(64) 3-[4-(4-hydroxy-1-cyclohexen-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(65) 3-(4-aminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(66) 3-[4-(N,N-dimethylamino)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(67) 3-[4-(2-hydroxyethyl)aminophenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(68) 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(69) 3-(4-ethylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(70) 3-(4-propylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(71) 3-(4-ethylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(72) 3-(4-propylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(73) 3-(4-butylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(74) 3-(4-sulfonamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(75) 3-[(4-morpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(76) 3-[(4-thiomorpholinyl)sulfonylphenyl]-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(77) 3-[(1,1-dioxythiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(78) 3-(4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(79) 3-(4-ethylsulfonylaminoethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(80) 3-(4-ethylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(81) 3-(4-propylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(82) 3-[4-(N,N-diethylamino)sulfonylmethylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(83) 3-[4-(tetrahydropyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(84) 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(85) 3-(4-ethylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(86) 3-(4-propylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(87) 3-(4-ethylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(88) 3-(4-propylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(89) 3-(4-butylaminocarbonylmethylphenyl)-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(90) 3-(4-methylsulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(91) 3-(3-chloro-4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(92) 3-(3-chloro-4-propylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(93) 3-(4-morpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(94) 3-(4-thiomorpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(95) 3-[4-(3-oxazolidinone)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(96) 3-[4-(4,4-ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(97) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxypiperidin-1-yl)phenyl]isoquinoline,

(98) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-methoxypiperidin-1-yl)phenyl]isoquinoline,

(99) 3-[2-(4-acetylpiperazin-1-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(100) 3-[4-(4-acetylpiperazin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(101) 3-(2-methoxybenzyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(102) 3-[α-methyl-(4-methoxybenzyl)]-1-(4-ethylpiperazin-

1-yl)isoquinoline,

(103) 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(104) 3-[α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(105) 3-[α-methyl-α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(106) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline,

(107) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenethyl]isoquinoline,

(108) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenethyl]isoquinoline,

(109) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenethyl]isoquinoline,

(110) 1-(1-ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline,

(111) 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(112) 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(113) 3-(4-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(114) 3-(6-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(115) 3-[4-(2-hydroxyethoxy)indan-1-yl)-1-(4-

ethylpiperazin-1-yl)isoquinoline,

(116) 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(117) 3-(7-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(118) 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(119) 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(120) 3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(121) 3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(122) 3-(3-hydroxymethylchroman-6-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(123) 1-(4-ethylpiperazin-1-yl)-3-(2-pyridyl)isoquinoline,

(124) 1-(1-ethylpiperazin-4-yl)-3-[5-(2-hydroxyethoxy)pyridin-2-yl]isoquinoline,

(125) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline,

(126) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline,

(127) 1-(1-ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline,

(128) 3-(2-propylcarbonylaminopyridin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(129) 3-[(2-methylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(130) 3-[(2-ethylsulfonylpyridin)-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(131) 1-(1-ethylpiperazin-4-yl)-3-(2-butylpyridin-5-yl)isoquinoline,

(132) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-fluoropropyl)pyridin-2-yl)isoquinoline,

(133) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-fluoropropyl)pyridin-5-yl]isoquinoline,

(134) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline,

(135) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline,

(136) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxybutyl)pyridin-5-yl]isoquinoline,

(137) 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline,

(138) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline,

(139) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline,

(140) 1-(1-ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline,

(141) 1-(1-ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline,

(142) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline,

(143) 1-(1-ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline,

(144) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline,

(145) 1-(1-ethylpiperazin-4-yl)-3-{2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl}isoquinoline,

(146) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline,

(147) 1-(4-ethylpiperazin-1-yl)-3-[2-(morpholin-4-yl)pyridin-5-yl]isoquinoline,

(148) 1-(4-ethylpiperazin-1-yl)-3-[5-(morpholin-4-yl)pyridin-2-yl]isoquinoline,

(149) 3-[2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(150) 1-(4-ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline,

(151) 1-(4-ethylpiperazin-1-yl)-3-[2-(S-oxythiomorpholin-4-yl)pyridin-5-yl]isoquinoline,

(152) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]isoquinoline,

(153) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-methoxypiperidin-1-yl)pyridin-5-yl]isoquinoline,

(154) 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxymethylpiperidin-1-yl)pyridin-5-yl]isoquinoline,

(155) 3-[2-(5,6-dihydro-2H-pyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(156) 3-[2-(tetrahydropyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(157) 3-[4-[3-(3-pyridyl)propoxy]phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(158) 1-(1-ethylpiperazin-4-yl)-3-(1-phenylpiperazin-4-yl)isoquinoline,

(159) 1-(1-ethylpiperazin-4-yl)-3-[1-(2-pyridyl)piperazin-4-yl]isoquinoline,

(160) 3-[4-(4-morpholinyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(161) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline,

(162) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline,

(163) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline,

(164) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-4-yl]isoquinoline,

(165) 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-5-yl)isoquinoline,

(166) 3-[2-(tetrahydropyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(167) 1-(1-ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline,

(168) 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline,

(169) 1-(1-ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline,

(170) 1-(1-ethylpiperazin-4-yl)-3-[(1-hydroxypropyl)thiazol-5-yl]isoquinoline,

(171) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline,

(172) 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)thiazol-5-yl]isoquinoline,

(173) 1-(1-ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)thiazol-5-yl]isoquinoline,

(174) 3-(2-propylcarbonylaminopyrimidin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline,

(175) 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-4-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(176) 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(177) 1-(1-ethylpiperazin-4-yl)-3-(phenylethynyl)isoquinoline,

(178) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenyl)ethynylisoquinoline,

(179) 1-(1-ethylpiperazin-4-yl)-3-(2-pyridyl)ethynylisoquinoline,

(180) 3-[3-(4-morpholinyl)-1-propynyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(181) 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-1-propynyl)isoquinoline,

(182) 1-(1-ethylpiperazin-4-yl)-3-(4-phenyl-1-butynyl)isoquinoline,

(183) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenylethynyl]isoquinoline,

(184) 1-(1-ethylpiperazin-4-yl)-3-benzoylethynylisoquinoline,

(185) 1-(1-ethylpiperazin-4-yl)-3-(2,4-dimethoxyphenylethynyl)isoquinoline,

(186) 1-(1-ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)-5-pyridyl]ethynylisoquinoline,

(187) 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenyl]ethynylisoquinoline,

(188) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)-2-pyridyl]ethynylisoquinoline,

(189) 1-(1-ethylpiperazin-4-yl)-3-(trans-2-phenylethenyl)isoquinoline,

(190) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-methoxyphenyl)ethenyl]isoquinoline,

(191) 1-(1-ethylpiperazin-4-yl)-3-[cis-2-(4-methoxyphenyl)ethenyl]isoquinoline,

(192) 1-(1-ethylpiperazin-4-yl)-3-(cis-1-methyl-2-phenylethenyl)isoquinoline,

(193) 1-(1-ethylpiperazin-4-yl)-3-(trans-1-methyl-2-phenylethenyl)isoquinoline,

(194) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-hydroxyethoxyphenyl)ethenyl]isoquinoline,

(195) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-methoxyphenyl)ethenyl]isoquinoline,

(196) 1-(1-ethylpiperazin-4-yl)-3-(trans-2-methyl-2-phenylethen-1-yl)isoquinoline,

(197) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-fluorophenyl)ethenyl]isoquinoline,

(198) 1-(1-ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline,

(199) 1-(1-ethylpiperazin-4-yl)-3-{trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl}isoquinoline,

(200) 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(201) 3-[(E)-2-(4-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(202) 3-[(E)-2-(2-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(203) 3-[(E)-2-(4-methylsulfonylmethylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(204) 3-{(E)-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(205) 3-{(E)-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(206) 3-{(E)-2-methyl-2-[4-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(207) 3-{(E)-2-methyl-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(208) 3-[(E)-2-methoxymethyl-2-phenylethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(209) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-pyridyl)ethenyl]isoquinoline,

(210) 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-pyridyl)ethenyl]isoquinoline,

(211) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-methoxy)phenyl-2-propenyl]isoquinoline,

(212) 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenyl-1-propenyl]isoquinoline,

(213) 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(214) 3-{(E)-2-[3-(4-morpholinyl)pyridazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(215) 3-{(E)-2-[4-(4-morpholinyl)pyrimidin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(216) 3-{(E)-2-[2-(4-morpholinyl)pyrazin-6-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline,

(217) 3-[1-(4-methoxyphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(218) 1-(1-ethylpiperazin-4-yl)-N-phenyl-3-isoquinolinecarboxamide,

(219) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyanilinomethyl)isoquinoline,

(220) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxybenzylamino)isoquinoline,

(221) 1-(1-ethylpiperazin-4-yl)-4-methoxy-3-(4-methoxyphenyl)isoquinoline,

(222) 1-(1-ethylpiperazin-4-yl)-5-methyl-3-(4-methoxyphenyl)isoquinoline,

(223) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-6-fluoroisoquinoline,

(224) 1-(1-ethylpiperazin-4-yl)-6-fluoro-3-(4-methoxyphenyl)isoquinoline,

(225) 1-(1-ethylpiperazin-4-yl)-6-methyl-3-(4-methoxyphenyl)isoquinoline,

(226) 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-trifluoromethylphenyl)isoquinoline,

(227) 1-(4-ethylpiperazin-1-yl)-6-methoxy-3-(4-methoxyphenyl)isoquinoline,

(228) 1-(1-ethylpiperazin-4-yl)-7-methyl-3-(4-methoxyphenyl)isoquinoline,

(229) 1-(4-ethylpiperazin-1-yl)-7-fluoro-3-(4-methoxyphenyl)isoquinoline,

(230) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]-7-fluoroisoquinoline,

(231) 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-phenylisoquinoline,

(232) 1-(4-ethylpiperazin-1-yl)-7-methoxy-3-(2-methoxyphenyl)isoquinoline,

(233) 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-(4-methoxyphenyl)isoquinoline,

(234) 1-(1-ethylpiperazin-4-yl)-8-fluoro-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(235) 1-(1-ethylpiperazin-4-yl)-8-methoxy-3-(4-methoxyphenyl)isoquinoline,

(236) 1-(1-propylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(237) 1-(1-propylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(238) 1-(1-isopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(239) 1-(1-cyclopropylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(240) 1-(1-allylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(241) 1-[1-(2-fluoroethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(242) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-(4-methoxyphenyl)isoquinoline,

(243) 3-(4-ethylsulfonylaminomethylphenyl)-1-[4-(2-hydroxyethyl)piperazin-1-yl]isoquinoline,

(244) 8-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)pyrido[2,3-c]pyridine,

(245) 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxyethoxy)phenyl]-1,7-naphthyridine,

(246) 8-(1-ethylpiperazin-4-yl)-6-{4-[(S)-2-hydroxypropoxy]phenyl}-1,7-naphthyridine,

(247) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxypropyl)phenyl]-1,7-naphthyridine,

(248) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]-1,7-naphthyridine,

(249) 8-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxy-1-fluoropropyl)phenyl]-1,7-naphthyridine,

(250) 8-(1-ethylpiperazin-4-yl)-6-[4-(2-hydroxy-2-methylpropoxy)phenyl]-1,7-naphthyridine,

(251) 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenyl)-2,6-naphthyridine,

(252) 5-(1-ethylpiperazin-4-yl)-7-(4-methoxyphenyl)-1,6-naphthyridine,

(253) 5-[4-(2-hydroxyethoxy)phenyl]-7-(4-methylpiperazin-1-yl)thieno[2,3-c]pyridine,

(254) 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxypentyl)phenyl]thieno[2,3-c]pyridine,

(255) 7-(1-ethylpiperazin-4-yl)-5-[4-(1-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine,

(256) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-1-fluoropropyl)phenyl]thieno[2,3-c]pyridine,

(257) 5-[4-(3-hydroxypropyl)-3-chlorophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(258) 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(259) 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyethoxyphenyl)thieno[2,3-c]pyridine,

(260) 7-(1-ethylpiperazin-4-yl)-5-[4-(2-hydroxy-2-methylpropoxy)phenyl]thieno[2,3-c]pyridine,

(261) 5-[3-(3-hydroxypropyl)-4-methoxyphenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(262) 5-[4-(3-hydroxypropyl)-3-cyanophenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(263) 5-[2-(4-morpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(264) 5-[2-(4-thiomorpholinyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(265) 5-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(266) 5-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(267) 5-[2-(2-methoxyethoxy-2-methyl)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(268) 5-[2-(2-hydroxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(269) 5-[2-(2-methoxyethoxy)pyridin-5-yl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(270) 5-[4-(4-hydroxycyclohexen-1-yl)phenyl]-7-(4-ethylpiperazin-1-yl)thieno[2,3-c]pyridine,

(271) 7-(1-ethylpiperazin-4-yl)-5-(4-pentanoylphenyl)thieno[2,3-c]pyridine,

(272) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-methylbutanoyl)phenyl]thieno[2,3-c]pyridine,

(273) 7-(1-ethylpiperazin-4-yl)-5-[4-(N-cyclohexylamide)phenyl]thieno[2,3-c]pyridinecarboxamide,

(274) 7-(1-ethylpiperazin-4-yl)-5-[4-(pyrrolidinyl-1-carbonyl)phenyl]thieno[2,3-c]pyridine,

(275) 5-[4-(2-hydroxyethoxy)phenyl]-7-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(276) 5-(4-methoxyphenyl)-7-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[2,3-c]pyridine,

(277) 4-(4-ethylpiperazin-1-yl)-6-(4-methoxyphenyl)thieno[3,4-c]pyridine,

(278) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,4-c]pyridine,

(279) 4-(4-methylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(280) 4-(4-ethylpiperazin-1-yl)-6-(4-hydroxyphenyl)thieno[3,2-c]pyridine,

(281) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxyethyl)phenyl]thieno[3,2-c]pyridine,

(282) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxypropyl)phenyl]thieno[3,2-c]pyridine,

(283) 4-(4-ethylpiperazin-1-yl)-6-[4-(1-hydroxybutyl)phenyl]thieno[3,2-c]pyridine,

(284) 4-(1-ethylpiperazin-4-yl)-6-[3-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(285) 4-(1-ethylpiperazin-4-yl)-6-[4-(3-hydroxybutyl)phenyl]thieno[3,2-c]pyridine,

(286) (4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(287) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(288) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-methylpiperazin-1-yl)thieno[3,2-c]pyridine,

(289) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-propylpiperazin-1-yl)thieno[3,2-c]pyridine,

(290) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine,

(291) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[3,2-c]pyridine,

(292) 6-[4-(4-methyl-4-hydroxypentyloxy)phenyl]-4-(4-ethylpiperazin-1-yl)thieno[3,2-c]pyridine,

(293) 4-(4-propylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(294) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-fluoroethyl)piperazin-1-yl)thieno[3,2-c]pyridine,

(295) 4-[4-(2-fluoroethyl)piperazin-1-yl]-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(296) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-hydroxyethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(297) 6-[4-(2-methyl-2-hydroxypropoxy)phenyl]-4-[4-(2-phenylethyl)piperazin-1-yl]thieno[3,2-c]pyridine,

(298) 7-(1-ethylpiperazin-4-yl)-5-[3-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine,

(299) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropyl)phenyl]furo[2,3-c]pyridine,

(300) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxybutyl)phenyl]furo[2,3-c]pyridine,

(301) 7-(1-ethylpiperazin-4-yl)-5-[4-(2-hydroxyethoxy)phenyl]furo[2,3-c]pyridine,

(302) 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine,

(303) 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxy-1-methylethoxy]phenyl}furo[2,3-c]pyridine,

(304) 7-(1-ethylpiperazin-4-yl)-5-{4-[(S)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine,

(305) 7-(1-ethylpiperazin-4-yl)-5-{4-[(R)-2-hydroxypropoxy]phenyl}furo[2,3-c]pyridine,

(306) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxy-3-methylbutoxy)phenyl]furo[2,3-c]pyridine,

(307) 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[4-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine,

(308) 7-(1-ethylpiperazin-4-yl)-5-{trans-2-[2-(2-hydroxyethoxy)phenyl]ethenyl}furo[2,3-c]pyridine,

(309) 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxy-2-methylpropoxy)phenyl]isoquinoline,

(310) 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-3-hydroxy-1-propynyl)isoquinoline,

(311) 1-(1-ethylpiperazin-4-yl)-8-methyl-3-(4-methoxyphenyl)isoquinoline,

(312) 1-(1-ethylpiperazin-4-yl)-4-methyl-3-(4-methoxyphenyl)isoquinoline,

(313) 1-[1-(2-cyanoethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(314) 1-[1-(carbamoylmethyl)piperazin-4-yl]-3-(4-methoxyphenyl)isoquinoline,

(315) 1-(4-ethylsulfonylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(316) 4-piperidinyl-6-[4-(2-methyl-2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(317) 7-(1-ethylpiperazin-4-yl)-5-[4-(3-hydroxypropoxy)phenyl]furo[2,3-c]pyridine,

(318) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(319) 1-{N-[2-(2-dimethylamino)ethyl]-N-methylamino}-3-(4-methoxyphenyl)isoquinoline,

(320) 1-(4-morpholinyl)-3-(4-methoxyphenyl)isoquinoline,

(321) 1-(1-ethyl-2-pyrrolidinyl)methylamino-3-(4-methoxyphenyl)isoquinoline,

(322) 3-(4-methoxyphenyl)-1-[2-(2-pyridyl)ethyl]aminoisoquinoline,

(323) 1-[2-(4-morpholinyl)ethyl]amino-3-(4-methoxyphenyl)isoquinoline,

(324) 1-(1-imidazolyl)-3-(4-methoxyphenyl)isoquinoline,

(325) 1-[4-(piperidin-1-yl)piperidin-1-yl]-3-(4-methoxyphenyl)isoquinoline,

(326) 1-(1,4,5,6-tetrahydropyrimidin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(327) 1-(1-ethylhomopiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline,

(328) 3-(4-methoxyphenyl)-1-(4-ethylpiperazin-1-yl)methylisoquinoline,

(329) 1-(4-ethylpiperazin-1-yl)-3-[3-(2-hydroxyethoxy)phenyl]isoquinoline,

(330) 1-(4-ethylpiperazin-1-yl)-3-(4-ethoxyphenyl)isoquinoline,

(331) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropoxy)phenyl]isoquinoline,

(332) 1-(4-ethylpiperazin-1-yl)-3-(3,4-ethylenedioxyphenyl)isoquinoline,

(333) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-methoxypropyl)phenyl]isoquinoline,

(334) 1-(4-ethylpiperazin-1-yl)-3-[4-(n-butyl)phenyl]isoquinoline,

(335) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxypyridin-2-yl)isoquinoline,

(336) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dioxolan-2-ylmethyloxy)phenyl]isoquinoline,

(337) 1-(4-ethylpiperazin-1-yl)-3-[4-(2,3-dihydroxypropoxy)phenyl]isoquinoline,

(338) 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylmethoxyphenyl)isoquinoline,

(339) 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethoxyphenyl)isoquinoline,

(340) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-3-methoxyphenyl]isoquinoline,

(341) 1-(4-ethylpiperazin-1-yl)-3-(4-methylthiophenyl)isoquinoline,

(342) 1-(4-ethylpiperazin-1-yl)-3-(4-methylsulfonylphenyl)isoquinoline,

(343) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-3-methoxypropoxy)phenyl]isoquinoline,

(344) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-5-yl)isoquinoline,

(345) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxy-1-methylethyl)phenyl]isoquinoline,

(346) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)carbamoyl]phenyl}isoquinoline,

(347) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)sulfamoyl]phenyl}isoquinoline,

(348) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyethyl)phenyl]isoquinoline,

(349) 1-(4-ethylpiperazin-1-yl)-3-[4-(propylsulfonyl)phenyl]isoquinoline,

(350) 1-(4-ethylpiperazin-1-yl)-3-{4-[(3-methoxypropyl)sulfonyl]phenyl}isoquinoline,

(351) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethyl)phenyl]isoquinoline,

(352) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)sulfonylphenyl]isoquinoline,

(353) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylsulfamoyl)phenyl]isoquinoline,

(354) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-methoxyethyl)sulfamoyl]phenyl}isoquinoline,

(355) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-fluoropropyl)sulfonylphenyl]isoquinoline,

(356) 1-(4-ethylpiperazin-1-yl)-3-[4-(pyrrolidin-1-yl)sulfonylphenyl]isoquinoline,

(357) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline,

(358) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylsulfamoyl)phenyl]isoquinoline,

(359) 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-diethylsulfamoyl)phenyl]isoquinoline,

(360) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(1-methylpropyl)sulfamoyl]phenyl}isoquinoline,

(361) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylsulfamoyl)phenyl]isoquinoline,

(362) 1-(4-ethylpiperazin-1-yl)-3-[4-(N,N-dimethylsulfamoyl)phenyl]isoquinoline,

(363) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-cyclopropylsulfamoyl)phenyl]isoquinoline,

(364) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-ethylcarbamoyl)phenyl]isoquinoline,

(365) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methylcarbamoyl)phenyl]isoquinoline,

(366) 1-(4-ethylpiperazin-1-yl)-3-[4-(ethylsulfonyl)phenyl]isoquinoline,

(367) 1-(4-ethylpiperazin-1-yl)-3-(3-fluoro-4-methoxyethoxyphenyl)isoquinoline,

(368) 1-(4-ethylpiperazin-1-yl)-3-(3,5-difluoro-4-methoxyethoxyphenyl)isoquinoline,

(369) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(370) 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(371) 1-(4-ethylpiperazin-1-yl)-3-[3,5-difluoro-4-(2-fluoroethoxy)phenyl]isoquinoline,

(372) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(N-ethylsulfamoyl)phenyl]isoquinoline,

(373) 1-[4-(2-hydroxyethyl)piperazin-1-yl]-3-[4-(propylsulfonyl)phenyl]isoquinoline,

(374) 1-(4-ethylpiperazin-1-yl)-3-(phenylthio)isoquinoline,

(375) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-oxopropyl)phenyl]isoquinoline,

(376) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxypropyl)phenyl]isoquinoline,

(377) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-2-

methylpropyl)phenyl]isoquinoline,

(378) 1-(4-ethylpiperazin-1-yl)-3-(2-pyridylthio)isoquinoline,

(379) 1-(4-ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline,

(380) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxyiminobutyl)phenyl]isoquinoline,

(381) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-methyl-N-propylcarbamoyl)phenyl]isoquinoline,

(382) 1-(4-ethylpiperazin-1-yl)-3-{4-[N-(2-hydroxyethyl)-N-methylcarbamoyl]phenyl}isoquinoline,

(383) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-1-methylpropyl)phenyl]isoquinoline,

(384) 1-(4-ethylpiperazin-1-yl)-3-[4-(N-propylcarbamoyl)-3-fluorophenyl]isoquinoline,

(385) 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-hydroxyethyl)phenyl]isoquinoline,

(386) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2-methylpropyl)phenyl]isoquinoline,

(387) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,2-dihydroxyethyl)phenyl]isoquinoline,

(388) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)phenyl]isoquinoline,

(389) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]isoquinoline,

(390) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-1,1-

dimethylpropyl)phenyl]isoquinoline,

(391) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-dihydroxy-2,2-dimethylpropyl)phenyl]isoquinoline,

(392) 1-(4-ethylpiperazin-1-yl)-3-{4-[4-(2-hydroxyethyl)tetrahydropyran-4-yl]phenyl}isoquinoline,

(393) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxymethylindan-5-yl)isoquinoline,

(394) 1-(4-ethylpiperazin-1-yl)-3-[(3,4-dihydroxymethyl)phenyl]isoquinoline,

(395) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,4-dioxan-2-yl)phenyl]isoquinoline,

(396) 1-(4-ethylpiperazin-1-yl)-3-[4-(tetrahydrofuran-2-yl)phenyl]isoquinoline,

(397) 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-hydroxycyclohexyl)phenyl]isoquinoline,

(398) 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxycyclohexyl)phenyl]isoquinoline,

(399) 1-(4-ethylpiperazin-1-yl)-3-[4-(tetrahydropyran-4-yl)methylphenyl]isoquinoline,

(400) 4-chloro-1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline,

(401) 1-(4-ethylpiperazin-1-yl)-3-[4-(cis-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline,

(402) 1-(4-ethylpiperazin-1-yl)-3-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]isoquinoline,

(403) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-

hydroxypropoxy)phenyl]isoquinoline,

(404) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxy-1-methylethoxy)phenyl]isoquinoline,

(405) 1-(4-ethylpiperazin-1-yl)-3-(2-methoxypyridin-4-yl)isoquinoline,

(406) 1-(4-ethylpiperazin-1-yl)-3-(2-benzyloxypyridin-4-yl)isoquinoline and 1-(4-ethylpiperazin-1-yl)-3-(2-chloropyridin-4-yl)isoquinoline,

(407) 1-(4-ethylpiperazin-1-yl)-3-[2-(2-methoxyethoxy)pyridin-4-yl]isoquinoline,

(408) 1-(4-ethylpiperazin-1-yl)-3-(4-carbamoylphenyl)isoquinoline,

(409) 1-(4-ethylpiperazin-1-yl)-3-[4-(cyclohexylhydroxymethyl)phenyl]isoquinoline,

(410) 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxytetrahydropyran-4-yl)phenyl]isoquinoline,

(411) 1-(4-ethylpiperazin-1-yl)-3-{4-[bis(1,3-thiazol-2-yl)hydroxymethyl]phenyl}isoquinoline,

(412) 1-(4-ethylpiperazin-1-yl)-3-[4-(1,3-thiazol-2-yl)hydroxymethylphenyl]isoquinoline,

(413) 1-(4-ethylpiperazin-1-yl)-3-[(3-pyridyl)hydroxymethyl]isoquinoline,

(414) 1-(4-ethylpiperazin-1-yl)-3-(1-indanon-5-yl)isoquinoline,

(415) 1-(4-ethylpiperazin-1-yl)-3-(1-hydroxyindan-5-yl)isoquinoline,

(416) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxy-3-methylbutyl)-3-fluorophenyl]isoquinoline,

(417) 1-(4-ethylpiperazin-1-yl)-3-[3-cyano-4-(2-hydroxyethoxy)phenyl]isoquinoline,

(418) 1-(4-ethylpiperazin-1-yl)-3-[3-(3-hydroxypropyl)phenyl]isoquinoline,

(419) 1-(4-ethylpiperazin-1-yl)-3-benzylisoquinoline,

(420) 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxy-2-phenylethyl)isoquinoline,

(421) 3-benzamide-1-(4-ethylpiperazin-1-yl)isoquinoline,

(422) 3-benzenesulfoneamide-1-(4-ethylpiperazin-1-yl)isoquinoline,

(423) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxybenzenesulfonamide)isoquinoline,

(424) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenoxymethyl)isoquinoline,

(425) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)-2-methoxyphenyl]isoquinoline,

(426) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxycyclohexyloxy)phenyl]isoquinoline,

(427) 4-(4-ethylpiperazin-1-yl)-2-(4-methoxyphenyl)quinazoline,

(428) 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)-7-azaisoquinoline,

(429) 7-(4-ethylpiperazin-1-yl)-5-[2-(3-hydroxypropyl)pyridin-5-yl]thieno[2,3-c]pyridine,

(430) 7-(4-ethylpiperazin-1-yl)-5-[3-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine,

(431) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxyethoxy)styryl]thieno[2,3-c]pyridine,

(432) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)phenyl]thieno[2,3-c]pyridine,

(433) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropyl)-3-methoxyphenyl]thieno[2,3-c]pyridine,

(434) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine,

(435) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropoxy)phenyl]thieno[2,3-c]pyridine,

(436) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropyl)phenyl]thieno[2,3-c]pyridine,

(437) 7-(4-ethylpiperazin-1-yl)-5-[3-chloro-4-(2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(438) 7-(4-ethylpiperazin-1-yl)-5-[4-(1-methyl-2-hydroxyethoxy)phenyl]thieno[2,3-c]pyridine,

(439) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-3-methylbutyl)phenyl]thieno[2,3-c]pyridine,

(440) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxybutyl)phenyl]thieno[2,3-c]pyridine,

(441) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2-methylpropyl)phenyl]thieno[2,3-c]pyridine,

(442) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-2,2-dimethylpropyl)phenyl]thieno[2,3-c]pyridine,

(443) 7-(4-ethylpiperazin-1-yl)-5-[4-(3-hydroxy-1,1-dimethylpropyl)phenyl]thieno[2,3-c]pyridine,

(444) 7-(4-ethylpiperazin-1-yl)-5-[4-(2-hydroxypropylthio)phenyl]thieno[2,3-c]pyridine,

(445) 7-(4-ethylpiperazin-1-yl)-5-(4-methanesulfonylphenyl)thieno[2,3-c]pyridine,

(446) 7-(4-ethylpiperazin-1-yl)-5-[4-(1-hydroxybutyl)phenyl]thieno[2,3-c]pyridine,

(447) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-methylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(448) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-ethylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(449) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-propylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(450) 7-(4-ethylpiperazin-1-yl)-5-(4-ethanesulfonylphenyl]thieno[2,3-c]pyridine,

(451) 7-(4-ethylpiperazin-1-yl)-5-(4-propanesulfonylphenyl)thieno[2,3-c]pyridine,

(452) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-butylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(453) 7-(4-ethylpiperazin-1-yl)-5-[4-(N-cyclopentylcarbamoyl)phenyl]thieno[2,3-c]pyridine,

(454) 7-(4-ethylpiperazin-1-yl)-5-[4-(cis-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine,

(455) 7-(4-ethylpiperazin-1-yl)-5-[4-(trans-4-hydroxytetrahydropyran-2-yl)phenyl]thieno[2,3-c]pyridine,

(456) 7-(4-ethylpiperazin-1-yl)-5-(2,3-dihydro-2-hydroxymethyl-2-methylbenzofuran-5-yl)phenyl]thieno[2,3-c]pyridine,

(457) 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclohexylhydroxymethyl)phenyl]thieno[2,3-c]pyridine,

(458) 7-(4-ethylpiperazin-1-yl)-5-[4-(cyclopentylhydroxymethyl)phenyl]thieno[2,3-c]pyridine,

(459) 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)thieno[2,3-c]pyridine,

(460) 4-(4-ethylpiperazin-1-yl)-6-[4-(1,3-dioxolan-2-yl)methoxyphenyl]thieno[3,2-c]pyridine,

(461) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(462) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine,

(463) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxy-1-methylethoxy)phenyl]thieno[3,2-c]pyridine,

(464) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-1-propynyl)phenyl]thieno[3,2-c]pyridine,

(465) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxypropyl)phenyl]thieno[3,2-c]pyridine,

(466) 4-(4-ethylpiperazin-1-yl)-6-[4-(3-hydroxy-3-methyl-1-butynyl)phenyl]thieno[3,2-c]pyridine,

(467) 7-(4-ethylpiperazin-1-yl)-5-(4-methoxyphenyl)furo[2,3-c]pyridine and

(468) 4-(4-ethylpiperazin-1-yl)-6-(4-

methoxyphenyl)furo[3,2-c]pyridine.

Among the condensed pyridine compound according to the present invention, those which are particularly preferable from the viewpoint of pharmacological effects or safety are, for example, the following ones:

(1) 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline,

(2) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline,

(3) 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline,

(4) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline,

(5) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline,

(6) 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline,

(7) 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline,

(8) 7-(4-ethylpiperazin-1-yl)-5-(4-hydroxyethoxyphenyl)thieno[2,3-c]pyridine,

(9) (4-ethylpiperazin-1-yl)-6-[4-(2-hydroxyethoxy)phenyl]thieno[3,2-c]pyridine,

(10) 4-(4-ethylpiperazin-1-yl)-6-[4-(2-hydroxypropoxy)phenyl]thieno[3,2-c]pyridine and

(11) 6-[4-(2-methyl-2-hydroxy)propoxyphenyl]-(4-

ethylpiperazin-1-yl)thieno[3,2-c]pyridine.

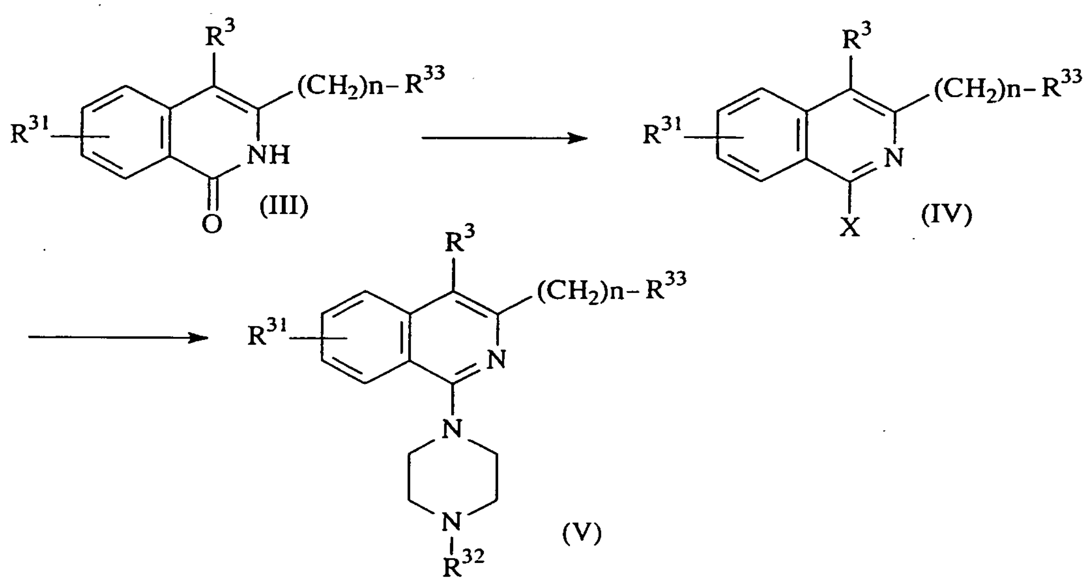
Although some of the condensed pyridine compound of the present invention occur as stereomers, either one of these stereomers or a mixture thereof may be used in the present invention without restriction. Similarly, either one of geometrical isomers or a mixture thereof may be employed herein without any restriction. In the case of polymorphic crystals, either one of the crystal forms or a mixture thereof may be used in the present invention without restriction, too. Moreover, use may be made of both anhydrides and hydrates.

The pharmacologically acceptable salts to be used in the present invention may be arbitrary salts of the condensed pyridine compound of the present invention without particular restriction. Examples thereof include inorganic acid addition salts such as hydrochlorides, sulfates, nitrates, hydrobromides, hydriodides, perchlorates and phosphates, organic acid addition salts such as oxalates, maleates, fumarates and succinates, sulfonic acid addition salts such as methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates and camphorsulfonates, and amino acid addition salts. Among all, it is preferable to use hydrochlorides and oxalates thereof.

Sequentially, a general process of producing the compound of the present invention will be described below, with no limitation. It can be prepared by other synthetic routes.

<u>(1) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is benzene ring</u>

The compound can be prepared by reacting isoquinolin-1-one compound (III) with a halogenating agent to give 1-halogenated isoquinoline compound (IV), and reacting the resulting compound which piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, $R^3$, $R^{31}$, $R^{32}$, $R^{33}$ and n have the same meanings as described above. X represents halogen atom.)



Herein, the isoquinolin-1-one compound (III) includes a great number of known compounds, which are available as industrial raw materials or reagents. And, These compound can be produced by methods described in known references.

The isoquinolin-1-one compound (III) can be halogenated by general methods. Herein, any type of halogenating agents can be used, with no limitation. Generally, phosphorus

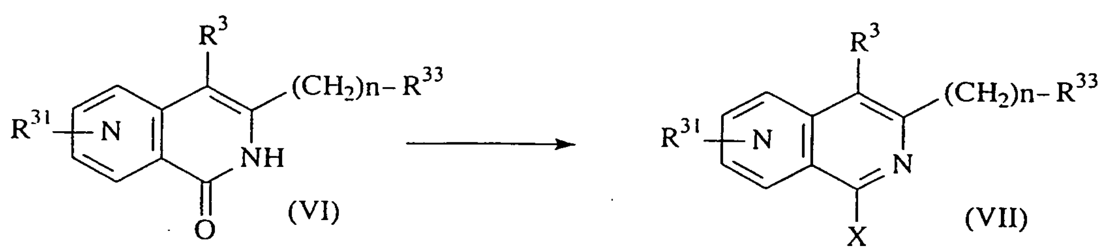
oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, sulfuryl chloride, oxazolyl chloride, phosphorus oxybromide, phosphorus tribromide and the like are used; among them, phosphorus oxychloride is preferable.

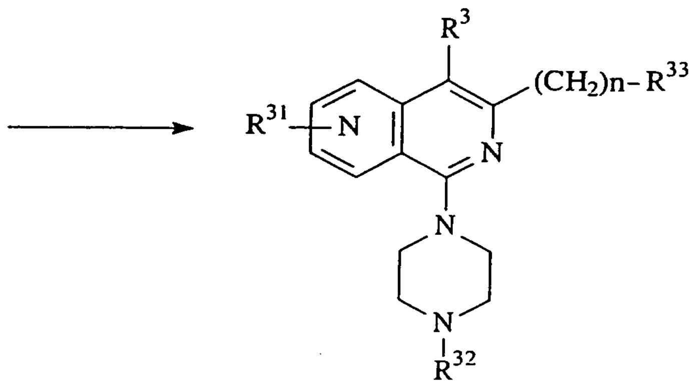
The reaction of the 1-halogenated isoquinoline compound (IV) with piperazine or 1-substituted piperazine can be effected by general methods for N-alkylation.

By chemically modifying the substituent of the 1-piperidylisoquinoline compound (V) thus prepared, furthermore, a novel 1-piperidylisoquinoline compound (V) can be derived.

(2) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is pyridine ring

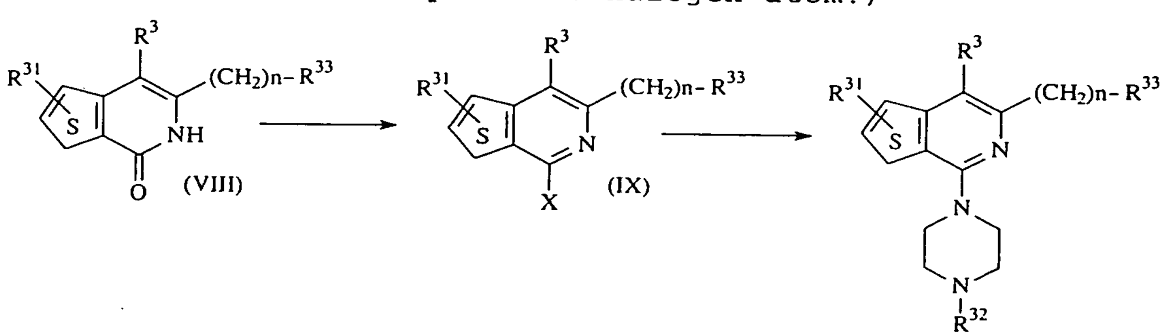
Also in this case, in the same manner as described above in (1), the compound can be prepared by reacting dihydropyridopyridin-8-one compound (VI) with a halogenating agent to give 8-halogenated pyridopyridine compound (VII), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, $R^3$, $R^{31}$, $R^{32}$, $R^{33}$ and n have the same meanings as described above. X represents halogen atom.)





(3) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is thiophene ring

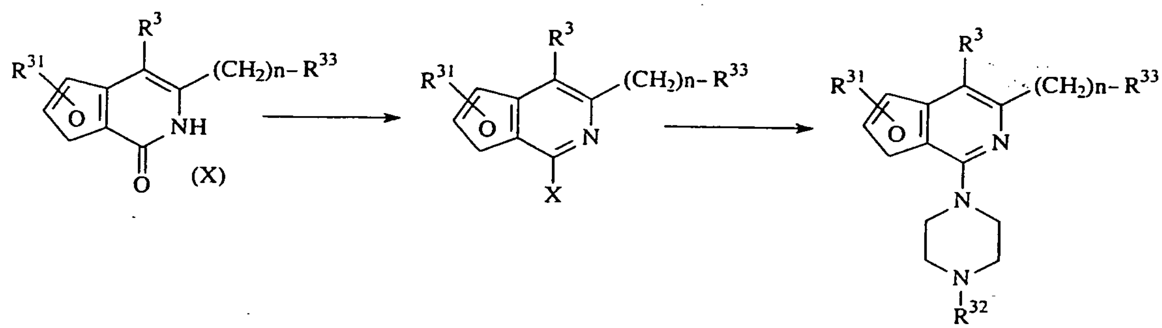
Also in this case, in the same manner as described above in (1) or (2), the compound can be prepared by reacting thienopyridopyridin-7-one compound (VIII) with a halogenating agent to give 7-halogenated thienopyridine compound (IX), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, $R^3$, $R^{31}$, $R^{32}$, $R^{33}$ and n have the same meanings as described above. X represents halogen atom.)



(4) The formula of the condensed pyridine compound (I) according to the present invention, in which ring A is furan ring

Also in this case, in the same manner as described above in any of (1) to (3), the compound can be prepared by reacting

furopyridin-7-one compound (X) with a halogenating agent to give 7-halogenated furopyridine compound (XI), and then reacting the resulting compound with piperazine or 1-substituted piperazine. (See the following formulae. In the formulae, $R^3$, $R^{31}$, $R^{32}$, $R^{33}$ and n have the same meanings as described above. X represents halogen atom.)



Examples of the dosage forms of the compounds of the present invention include oral preparations such as powders, fine granules, granules, tablets, coated tablets and capsules, external preparations such as ointments, patches and suppositories, and injections. These preparations may be produced by the conventional methods with the use of pharmaceutical carriers commonly employed in the art.

Namely, oral preparations may be produced by blending the 1,4-substituted cyclic amine derivative or a pharmacologically acceptable salt thereof with fillers optionally together with binders, disintegrating agents, lubricating agents, coloring agents, corrigents, etc. and then processing the resultant blends into powders, fine granules, granules, tablets, coated tablets, capsules, etc. by the conventional methods.

As the fillers, use may be made of, for example, lactose,

corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. As the binders, use may be made of, for example, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol/polyoxyethylene block polymers and meglumine. As the disintegrating agents, use may be made of, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin and calcium carboxymethylcellulose. As the lubricating agents, use may be made of, for example, magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. As the coloring agents, use may be made of those authorized as pharmaceutical additives. As the corrigents, use may be made of, for example, cocoa powder, mentha, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Needless to say, these tablets and granules may be appropriately coated with sugar, etc., if necessary.

Injections are produced by blending the condensed pyridine compound or a pharmacologically acceptable salt thereof with pH regulating agents, resolvents, tonicity agents, etc., optionally together with dissolution aids, stabilizers, etc. and processing the resultant blends into preparations by the conventional methods.

External preparations may be produced by the conventional

methods without restriction. As the bases, therefore, use can be made of various materials commonly used in drugs, quasi drugs, cosmetics, etc.

Particular examples of the base materials include animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. If needed, it is possible to further add pH regulating agents, antioxidants, chelating agents, antiseptics, fungicides, coloring agents, perfumes, etc., though the materials usable as the base in the external preparations of the present invention are not restricted thereto. If necessary, it is also possible to furthermore add other ingredients capable of inducing differentiation, blood flow accelerators, bactericides, antiinflammatory agents, cell activators, vitamins, amino acids, humectants, keratolytic agents, etc. The above materials may be added in such amounts as to give the concentrations thereof commonly employed in the production of external preparations.

The clinical dose of the condensed pyridine compound of the present invention or a pharmacologically acceptable salt thereof is not restricted but varies depending on the symptoms, severity, age, complications, etc. Also, the dose thereof varies depending on the type of the salt, administration route, etc. In general, these compounds are administered to an adult

in a dose of from 0.01 to 1000 mg, preferably from 0.1 to 500 mg and still preferably from 0.5 to 100 mg, per day orally, intravenously, as suppositories or percutaneously.

Next, the results of a binding test on the compounds of the present invention to serotonin 1A and serotonin 2 receptors will be given so as to illustrate the effects of the present invention. Moreover, the results of a binding test on these compounds to an $\alpha_1$ adrenalin receptor will be given so as to illustrate the safety thereof.

It is reported in, for example, the following publications that compounds with a serotonin antagonism are usable as medicament for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia:

(1) Saishin Igaku Jiten, 3rd impression of 1st edition, p. 809 "SEROTONIN", Iyaku Shuppan

(2) Stedman's Medical Dictionary, 24th edition, p. 1227 "serotonin", Williams & Wilkins

(3) Shinkei Shinpo, 37(3), 459 - 467, 1993.

(4) Iyaku Journal, 30(8), 2030 - 2068, 1994.

(5) DN & P, 5(8), 453 - 460, 1992.

(6) Annals of Neurology, 30(4), 533 - 541, 1991.

Compounds poor in the ability to bind to an $\alpha_1$ adrenalin receptor are medicines which would scarcely affect blood pressure in orthostatic hypotension, etc. and have a higher safety.

(1) Binding test on serotonin 1A, serotonin 2 and $\alpha_1$ adrenalin receptors

Method

(Reagent)

The following reagents were employed in this test.

1) Serotonin binoxalate (5-HT binoxalate, mfd. by Sigma Chemical Co.).

2) Methysergide maleate (mfd. by RBI).

As radioisotope-labeled compounds, use was made of the following reagents (mfd. by NEN).

3) [$^3$H] 8-Hydroxy-dipropylaminotetralin (8-OH-DPAT).

4) [$^3$H] Ketanserin hydrochloride.

5) [$^3$H] Prazosin.

These compounds and test compounds, when insoluble in water, were dissolved in ethanol and then diluted with distilled water so as to each give an ethanol concentration of 10%. Methysergide maleate was dissolved in distilled water before using.

(Animal)

Use was made of SD rats aged 6 to 8 weeks.

(Preparation of receptor source)

The rats were sacrificed by dcapitation to extirpate the cerebra. The hippocampus and cortex were separated therefrom and employed in the binding tests respectively on the serotonin 1A receptor and the serotonin 2 receptor.

The hippocampus was mixed with 50 times (on the wet weight

basis) as much a 0.32 M sucrose solution while the cortex was mixed with 10 times as much the same solution. Each mixture was homogenized by using a Teflon glass homogenizer and centrifuged at 1,000 × g for 10 min. The supernatant thus obtained was further centrifuged at 20,000 × g for 20 min. The obtained precipitate was re-suspended in 50 times (based on the intial wet weight; in the case of the hippocampus) or 10 times (in the case of the cortex) as much a 50 mM Tris hydrochloride (pH 7.4) and incubated at room temperature for 30 min. After centrifuging at 20,000 × g for 20 min, the obtained precipitate was further suspended and centrifuged twice each in the same manner. The precipitate thus obtained was suspended in 100 times (based on the initial wet weight; in the case of the hippocampus) or 20 times (in the case of the cortex) as much a 50 mM Tris hydrochloride solution (pH 7.4) to thereby give a receptor fraction. This receptor fraction was stored at -80°C until using.

(Binding test on [$^3$H] 8-hydroxy-dipropylaminotetralin)

To the receptor fraction of the hippocampus were added a test compound and 0.5 nM of [$^3$H] 8-hydroxy-dipropylamino-tetralin and the resultant mixture was incubated at room temperature for 30 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 10 μM of serotonin

binoxalate was referred to as the nonspecific binding.

(Binding test on [$^3$H] ketanserin)

To the receptor fraction of the cerebral cortex were added a test compound and 0.3 nM of [$^3$H] ketanserin and the resultant mixture was incubated at 37℃ for 15 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 1 μM of methysergide was referred to as the nonspecific binding.

$IC_{50}$ was calculated by the probit method, while Ki was determined in accordance with the following formula:

$$Ki = IC_{50}/(1 + c/Kd)$$

wherein c represents the concentration of the radioisotope-labeled compound, and Kd represents the dissociation constant of the radioisotope-labeled compound with respect to the receptor determined by Scatchard's analysis.

(Binding test on [$^3$H] prazosin)

To the receptor fraction of the cerebral cortex were added a test compound and about 0.2 nM of [$^3$H] prazosin and the resultant mixture was incubated at room temperature for 60 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding

detected in the presence of 10 μM of phentolamine was referred to as the nonspecific binding.

The following tables show the abilities of typical examples of the compounds of the present invention to bind to the serotonin (5HT)1A and serotonin (5HT)2 receptors, wherein the number of each compound corresponds to the number of Example described below. Also, comparison was made with cyproheptadine hydrochloride and cyclobenzaprine hydrochloride which were employed as positive controls having anti-serotonin effects.

| Example No. | 5HT1(nM) | 5HT2(nM) |
|---|---|---|
| 1 | 21.2 | 36.4 |
| 3 | 65 | 3.8 |
| 4 | 71 | 74.9 |
| 5 | 21 | 2.2 |
| 7 | 27.9 | 81.3 |
| 9 | 57 | 24.5 |
| 10 | 60 | 11 |
| 12 | 140 | 5.32 |
| 14 | 23 | 35 |
| 15 | 55.5 | 19.5 |
| 16 | 30 | 44 |
| 17 | 11.1 | 26.8 |

| | | |
|---|---|---|
| 19 | 6.9 | 1.6 |
| 20 | 14.5 | 2.6 |
| 21 | 17.2 | 4.3 |
| 22 | 9.4 | 1.5 |
| 23 | 16.8 | 6.4 |
| 24 | 11.7 | 7.4 |
| 25 | 21.5 | 3.4 |
| 26 | 8.5 | 55 |
| 27 | 29.42 | 2.47 |
| 28 | 24.4 | 9.1 |
| 29 | 9.6 | 3.5 |
| 30 | 10.7 | 6.3 |
| 31 | 10.7 | 30.3 |
| 32 | 10.1 | 7.8 |
| 33 | 7.9 | 10.9 |
| 34 | 23.5 | 17.3 |
| 35 | 35.3 | 5.7 |
| 36 | 18.8 | 3.9 |
| 38 | 20.8 | 75.7 |
| 39 | 26 | 4.9 |
| 40 | 26.7 | 3.1 |
| 41 | 40.1 | 45.6 |
| 42 | 33.1 | 4.4 |
| 43 | 29.3 | 66.6 |
| 44 | 55.4 | 9 |
| 45 | 45 | 1.1 |

| | | |
|---|---|---|
| 46 | 58 | 12.7 |
| 47 | 25.3 | 2.6 |
| 50 | 25.2 | 21.9 |
| 51 | 102.77 | 1.87 |
| 52 | 23.5 | 0.6 |
| 53 | 61.25 | 1.78 |
| 54 | 62.1 | 4.9 |
| 55 | 10.4 | 15.3 |
| 56 | 37.4 | 59.5 |
| 57 | 57.2 | 4.6 |
| 58 | 23.3 | 18.7 |
| 59 | 16.3 | 14.3 |
| 60 | 21.3 | 9.1 |
| 61 | 11.7 | 8.2 |
| 62 | 14.8 | 4 |
| 63 | 18.1 | 0.84 |
| 64 | 86.99 | 8.5 |
| 65 | 60.1 | 33.5 |
| 66 | 52.7 | 21.6 |
| 67 | 27.3 | 6.6 |
| 68 | 30.9 | 94.1 |
| 69 | 17.2 | 17.3 |
| 70 | 23.3 | 5.5 |
| 71 | 2 | 1.5 |
| 72 | 15 | 3.6 |
| 73 | 13 | 3.3 |

| | | |
|---|---|---|
| 74 | 4.6 | 7.7 |
| 75 | 7.7 | 10 |
| 76 | 5.7 | 8.9 |
| 77 | 13.6 | 90.5 |
| 78 | 0.56 | 1.9 |
| 79 | 5.8 | 23 |
| 80 | 0.8 | 16.3 |
| 81 | 1.1 | 15.1 |
| 82 | 0.2 | 10.8 |
| 83 | 75.6 | 4.3 |
| 84 | 72.1 | 0.9 |
| 85 | 18.7 | 9.7 |
| 86 | 11.7 | 5.3 |
| 87 | 16.9 | 17 |
| 88 | 9.4 | 11.7 |
| 89 | 6.3 | 10 |
| 90 | 4.5 | 12.9 |
| 91 | 1.1 | 1.6 |
| 92 | 0.9 | 0.7 |
| 93 | 10.8 | 56.7 |
| 94 | 6.4 | 41.2 |
| 95 | 7.8 | 21.2 |
| 96 | 138.4 | 0.1 |
| 97 | 34.7 | 13.3 |
| 98 | 61.6 | 2.7 |
| 99 | 3.5 | 6.2 |

| | | |
|---|---|---|
| 100 | 12.7 | 5.6 |
| 102 | 129.36 | 132.01 |
| 104 | 108.71 | 100.93 |
| 106 | 70 | 30.6 |
| 108 | 156.65 | 33.76 |
| 110 | 58.62 | 108.98 |
| 111 | 10.28 | 89.9 |
| 114 | 167.03 | 49.89 |
| 122 | 40.1 | 19.9 |
| 123 | 34 | 29.1 |
| 125 | 27.1 | 6.9 |
| 126 | 26.4 | 5.7 |
| 128 | 22.2 | 3 |
| 129 | 21.6 | 18.4 |
| 130 | 24.4 | 17 |
| 131 | 6.4 | 5.8 |
| 132 | 1.5 | 23.4 |
| 133 | 2.9 | 6.2 |
| 134 | 4.9 | 12.4 |
| 135 | 3.4 | 18.9 |
| 136 | 3.7 | 11.6 |
| 137 | 7.2 | 32.5 |
| 138 | 13.5 | 5.5 |
| 139 | 2.7 | 5.1 |
| 140 | 22.1 | 36.7 |
| 141 | 2.9 | 20.4 |

| | | |
|---|---|---|
| 142 | 3.3 | 15.2 |
| 143 | 2.2 | 17.4 |
| 144 | 4.8 | 12.4 |
| 145 | 7.5 | 3.7 |
| 146 | 170.5 | 2.9 |
| 147 | 6.5 | 1.7 |
| 148 | 6.33 | 7.85 |
| 149 | 37.2 | 21.8 |
| 150 | 10.7 | 0.8 |
| 151 | 7 | 79.2 |
| 152 | 6.1 | 12.4 |
| 153 | 12.9 | 1.5 |
| 154 | 1.6 | 8.8 |
| 155 | 19.98 | 4.34 |
| 156 | 10.93 | 0.01 |
| 157 | 29.7 | 4.9 |
| 158 | 0.41 | 1.08 |
| 159 | 0.65 | 13.25 |
| 160 | 22.2 | 0.7 |
| 161 | 10.7 | 23.8 |
| 162 | 10.7 | 84.7 |
| 163 | 25.1 | 19.2 |
| 164 | 9.38 | 11.88 |
| 165 | 32.58 | 25.38 |
| 166 | 81.89 | 11.49 |
| 170 | 3 | 25.4 |

| | | |
|---|---|---|
| 171 | 4.7 | 21.9 |
| 172 | 4.7 | 36.2 |
| 173 | 3.9 | 4.8 |
| 174 | 29.1 | 7.3 |
| 176 | 154.55 | 12.38 |
| 177 | 45 | 0.5 |
| 178 | 56.4 | 0.2 |
| 179 | 5.3 | 0.4 |
| 181 | 17.9 | 6.7 |
| 182 | 10 | 15.89 |
| 183 | 14.1 | 3.36 |
| 184 | 30.85 | 122.2 |
| 185 | 21.21 | 2 |
| 186 | 2.83 | 4.5 |
| 187 | 9.81 | 2.53 |
| 188 | 4.47 | 106.9 |
| 189 | 37.17 | 0.44 |
| 190 | 35 | 3.85 |
| 191 | 12.98 | 0.93 |
| 192 | 66.74 | 7.85 |
| 194 | 11.21 | 33.72 |
| 195 | 22.96 | 37.22 |
| 196 | 66.74 | 6.44 |
| 197 | 70.69 | 4.26 |
| 198 | 45.5 | 9.08 |
| 199 | 3.27 | 3.8 |

| | | |
|---|---|---|
| 200 | 77.3 | 7.33 |
| 201 | 35.9 | 2.96 |
| 202 | 14.61 | 2.22 |
| 203 | 5.5 | 0.52 |
| 204 | 25.46 | 18.54 |
| 205 | 33.15 | 0.98 |
| 206 | 77.12 | 2.59 |
| 207 | 22.23 | 17.95 |
| 208 | 91.61 | 7.62 |
| 209 | 3.28 | 2.35 |
| 210 | 6.56 | 3.95 |
| 211 | 5.17 | 40.2 |
| 213 | 21.1 | 31.82 |
| 214 | 15.59 | 7.59 |
| 215 | 51.93 | 20.86 |
| 216 | 16.55 | 15.53 |
| 219 | 2.99 | 5.92 |
| 220 | 0.53 | 2.01 |
| 233 | 200 | 1.97 |
| 234 | 128.78 | 1.11 |
| 243 | 13 | 6.7 |
| 244 | 27.14 | 78.55 |
| 245 | 109.44 | 72.17 |
| 246 | 86.99 | 13.91 |
| 247 | 25.08 | 28.72 |
| 248 | 42.98 | 31.57 |

| | | |
|---|---|---|
| 249 | 37.96 | 28.08 |
| 250 | 122.76 | 7.67 |
| 253 | 75.37 | 5.98 |
| 254 | 59.73 | 29.18 |
| 255 | 75.37 | 40.04 |
| 256 | 9.22 | 19.48 |
| 257 | 12.58 | 23.23 |
| 258 | 24.72 | 35.1 |
| 259 | 9.26 | 18.86 |
| 260 | 67.79 | 0.54 |
| 261 | 53.74 | 0.06 |
| 262 | 9.04 | 0.25 |
| 263 | 6.42 | 0.89 |
| 264 | 61.35 | 3.34 |
| 265 | 9.73 | 113.91 |
| 266 | 97.26 | 13.78 |
| 267 | 10.39 | 68.74 |
| 268 | 16.51 | 85.99 |
| 269 | 15.53 | 58.38 |
| 270 | 42.98 | 30.32 |
| 272 | 159.51 | 22.45 |
| 273 | 51.44 | 9.11 |
| 276 | 159.51 | 0.45 |
| 277 | 71.36 | 52.06 |
| 278 | 41.28 | 4.61 |
| 279 | 76.43 | 1.44 |

| | | |
|---|---|---|
| 281 | 15.03 | 16.92 |
| 282 | 10.79 | 6.46 |
| 283 | 5.71 | 6.43 |
| 284 | 91.86 | 75.86 |
| 285 | 22.18 | 1.96 |
| 286 | 6.95 | 3.95 |
| 287 | 27.91 | 0.87 |
| 288 | 80.94 | 0.14 |
| 290 | 54.87 | 1.35 |
| 291 | 43.3 | 1.44 |
| 292 | 68.62 | 22.45 |
| 298 | 1.72 | 5.37 |
| 299 | 0.37 | 30.14 |
| 300 | 0.49 | 9.06 |
| 301 | 9.15 | 12.73 |
| 302 | 0.53 | 30 |
| 303 | 0.53 | 44.42 |
| 304 | 15.44 | 19.42 |
| 305 | 18.47 | 33.12 |
| 306 | 47.73 | 0.82 |
| 307 | 7.7 | 11.47 |
| 308 | 6.49 | 19.46 |
| 309 | 91 | 0.01 |
| 310 | 4.4 | 10.18 |
| 317 | 12.24 | 105.36 |
| 329 | 31.6 | 73.6 |

| | | |
|---|---|---|
| 331 | 23.6 | 5.9 |
| 332 | 13.9 | 12.1 |
| 333 | 17.1 | 6.1 |
| 335 | 60.1 | 20.3 |
| 336 | 45.7 | 2.6 |
| 337 | 25.7 | 5.6 |
| 338 | 14.1 | 61.9 |
| 339 | 214 | 18.9 |
| 340 | 26.0 | 20.7 |
| 342 | 6.2 | 14.9 |
| 343 | 35.7 | 5.7 |
| 344 | 10.7 | 35.9 |
| 345 | 11.3 | 1.4 |
| 346 | 31.8 | 41.7 |
| 347 | 8.0 | 24.2 |
| 348 | 11.0 | 1.6 |
| 349 | 3.2 | 5.0 |
| 350 | 2.6 | 16.7 |
| 351 | 15.7 | 6.4 |
| 352 | 4.0 | 54.6 |
| 353 | 1.1 | 0.24 |
| 354 | 3.0 | 1.3 |
| 355 | 2.6 | 4.9 |
| 356 | 2.1 | 24.2 |
| 357 | 2.8 | 0.58 |
| 358 | 6.4 | 19.1 |

| | | |
|---|---|---|
| 359 | 6.1 | 3.2 |
| 360 | 2.0 | 1.5 |
| 361 | 3.5 | 2.6 |
| 362 | 4.5 | 24.1 |
| 363 | 3.5 | 0.61 |
| 364 | 21.7 | 3.9 |
| 365 | 26.2 | 9.9 |
| 366 | 3.8 | 7.2 |
| 367 | 55.2 | 3.3 |
| 368 | 32.0 | 9.1 |
| 369 | 28.2 | 2.5 |
| 370 | 23.9 | 3.4 |
| 371 | 41.0 | 4.3 |
| 374 | 44.5 | 24.7 |
| 375 | 30.5 | 7.6 |
| 376 | 19.5 | 6.3 |
| 377 | 28.5 | 16.5 |
| 378 | 42.7 | 95.2 |
| 380 | 31.2 | 23.0 |
| 381 | 11.1 | 27.3 |
| 383 | 7.4 | 3.4 |
| 384 | 27.3 | 0.1 |
| 385 | 14.8 | 21.6 |
| 386 | 8.9 | 2.4 |
| 387 | 25.1 | 24.7 |
| 388 | 21.5 | 0.7 |

| | | | |
|---|---|---|---|
| 389 | | 14.2 | 7.3 |
| 390 | | 7.5 | 11.1 |
| 391 | | 3.6 | 12.8 |
| 393 | | 13.1 | 1.8 |
| 394 | | 10.7 | 32.9 |
| 395 | | 37.3 | 4.8 |
| 396 | | 50.4 | 2.6 |
| 397 | | 53.3 | 0.9 |
| 398 | | 8.0 | 5.9 |
| 399 | | 53.0 | 17.2 |
| 401 | | 31.3 | 3.4 |
| 402 | | 23.7 | 2.1 |
| 403 | | 28.35 | 0.78 |
| 404 | | 18.76 | 1.07 |
| 405 | | 22.6 | 10.2 |
| 406 | 2-Benzyloxy | 46.0 | 88.1 |
| | 2-chloro | 12.2 | 11.1 |
| 407 | | 17.8 | 26.1 |
| 408 | | 19.8 | 36.3 |
| 409 | | 16.4 | 9.7 |
| 410 | | 21.1 | 2.1 |
| 412 | | 19.1 | 41.4 |
| 414 | | 17.3 | 4.2 |
| 415 | | 3.6 | 11.6 |
| 416 | | 31.2 | 0.7 |
| 417 | | 13.4 | 4.5 |

| | | |
|---|---|---|
| 418 | 54.5 | 17.4 |
| 419 | 94.8 | 16.4 |
| 420 | 117.4 | 22.4 |
| 421 | 9.47 | 129.2 |
| 422 | 5.32 | 175.3 |
| 423 | 9.81 | 332.47 |
| 424 | 61.6 | 1.93 |
| 425 | 320.58 | 2.55 |
| 426 | 132.70 | 7.10 |
| 427 | 80.94 | 300.37 |
| 430 | 2.48 | 11.68 |
| 431 | 1.98 | 2.11 |
| 432 | 1.98 | 28.48 |
| 433 | 20.63 | 3.53 |
| 434 | 64.88 | 60.48 |
| 435 | 61.18 | 1.14 |
| 436 | 8.64 | 26.03 |
| 437 | 30.49 | 18.11 |
| 438 | 62.94 | 18.83 |
| 439 | 44.18 | 6.03 |
| 440 | 21.83 | 0.72 |
| 441 | 15.23 | 0.41 |
| 442 | 23.23 | 2.66 |
| 443 | 10.24 | 1.85 |
| 444 | 43.16 | 11.98 |
| 445 | 5.46 | 90.37 |

| | | |
|---|---|---|
| 446 | 12.20 | 29.96 |
| 448 | 22.60 | 345.80 |
| 449 | 24.04 | 43.79 |
| 450 | 6.89 | 15.16 |
| 451 | 7.72 | 37.86 |
| 452 | 19.61 | 7.04 |
| 453 | 22.18 | 45.39 |
| 454 | 67.41 | 26.53 |
| 455 | 50.33 | 39.99 |
| 456 | 63.33 | 16.21 |
| 457 | 63.33 | 280.93 |
| 458 | 75.37 | 93.12 |
| 459 | 107.86 | 60.15 |
| 460 | 5.32 | 175.3 |
| 461 | 0.17 | 15.21 |
| 462 | 4.83 | 2.84 |
| 463 | 6.98 | 20.86 |
| 464 | 47.81 | 1.40 |
| 465 | 6.28 | 7.11 |
| 466 | 49.8 | 1.0 |
| 467 | 20.55 | 93.11 |
| Cyproheptadine | 29.5 | 1.68 |
| Cyclobenzaprine | 25 | 29 |

Subsequently, the abilities of typical examples of the compounds of the present invention to bind to the $\alpha_1$ adrenalin receptor were evaluated by the test method described above. The following table shows the results, wherein the number of each compound corresponds to the number of Example described below.

| Example No. | $\alpha 1$ (nM) |
|---|---|
| 1 | >2000 |
| 7 | 521 |
| 12 | 4111 |
| 19 | 373 |
| 20 | 868 |
| 21 | 636 |
| 22 | 3095 |
| 23 | 1253 |
| 29 | 668 |
| 32 | 500 |
| 33 | 758 |
| 36 | 1220 |
| 42 | 2450 |
| 45 | 1220 |
| 52 | 555 |
| 63 | 252 |
| 70 | 1260 |
| 73 | 699 |

| | |
|---|---|
| 109 | >2000 |
| 123 | 553 |
| 126 | 382 |
| 139 | 374 |
| 160 | 536 |
| 173 | 284 |
| 179 | 208 |
| 181 | 920 |
| 183 | 577 |
| 185 | 741 |
| 187 | 969 |
| 200 | 755 |
| 202 | >2000 |
| 220 | 3803 |
| 242 | 1788 |
| 259 | 405 |
| 281 | 345 |
| 286 | 305 |
| 289 | 1306 |
| 300 | >2000 |
| 331 | 721.5 |
| 393 | 241.8 |
| 416 | 173.5 |
| Cyproheptadine | 1900 |

The above results indicate that the condensed pyridine compound of the present invention are useful as medicaments with a serotonin antagonism and have clinical usefulness and a high safety, in particular, those for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

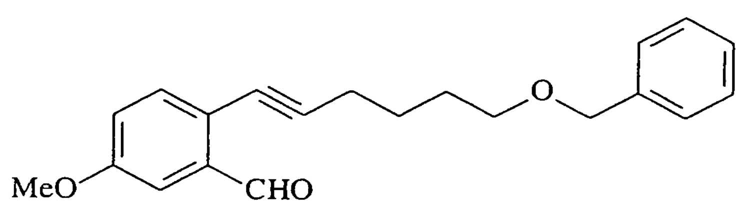
Moreover, it is also evident that the compounds of the present invention are superior in safety, since they have low abilities to bond to the $\alpha 1$ adrenalin receptor and scarcely affect blood pressure.

Next, to illustrate the present invention in detail, Examples will be given below. However, it is needless to say that the present invention is not restricted thereto.

Examples

Example 1 Synthesis of 3-(4-benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride

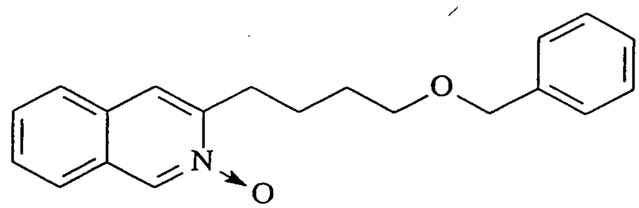
(1-1) 2-[2-(4-Benzyloxybutyl)ethynyl]-5-methoxybenzaldehyde




6-Benzyloxy-1-hexyne (5.60 g) and 2-bromo-benzaldehyde (2.90 g) were reacted in dimethylformamide (30 ml), in the presence of dichloro-bis-triphenylphosphinepalladium (0.40 g), cuprous iodide (0.20 g) and triethylamine (2.5 ml) in nitrogen

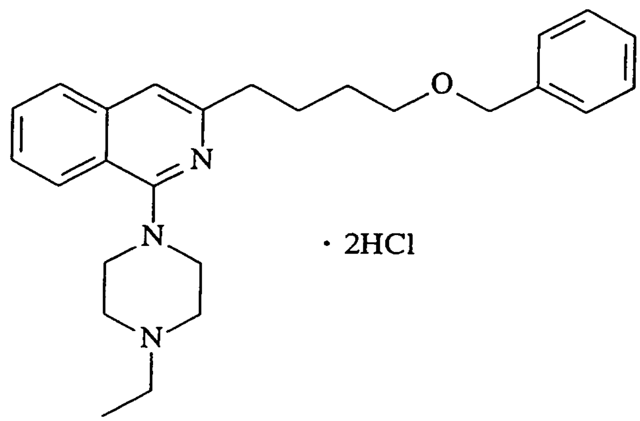
atmosphere at 50°C for 6 hr. The resulting reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 2.60 g of the title compound as a pale yellow oil.

(1-2) 3-(4-Benzyloxybutyl)isoquinoline-2-oxide



2-[2-(4-Benzyloxybutyl)ethynyl]-5-methoxybenzaldehyde (2.60 g), hydroxylamine hydrochloride (0.63 g) and sodium acetate (0.78 g) were reacted in ethanol (30 ml) at 60°C for 2 hr. Potassium carbonate (2.0 g) and water (5 ml) were added to the resulting reaction mixture, which was then heated under reflux for 12 hr. The reaction solution was evaporated, and the resulting residue was extracted with methylene chloride, washed with brine, and then dried. The solvent was removed and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 2.0 g of the title compound as a brown amorphous.

(1-3) 3-(4-Benzyloxybutyl)-1-(4-ethylpiperazin-1-yl)isoquinoline



3-(4-Benzyloxybutyl)isoquinoline-2-oxide (2.0 g) and phosphorous oxychloride (5 ml) were reacted at 110 °C for 2 hr. The reaction solution was evaporated, to the resulting residue were added ethyl acetate and aqueous solution of saturated sodium bicarbonate, and the resulting organic layer was washed with water and brine. The organic layer was dried over magnesium sulfate followed by evaporating the solvent. The resulting 1-chloro-3-(4-benzyloxybutyl)isoquinoline obtained as a yellow oil was reacted with N-ethylpiperazine (5 ml) and potassium carbonate (0.5 g) at 120 °C for 5 hr. The reaction solution was then cooled and then partitioned by adding ethyl acetate and water thereto. The resulting organic layer was washe with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give 1.32 g of the free compound of the title compound as a pale yellow oil.

Free compound:

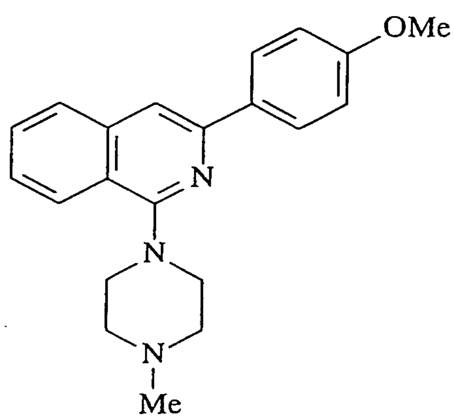
$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 1.64-

1.75(m,2H), 1.80-1.92(m,2H), 2.54(q,J=7.2Hz,2H), 2.74(m,4H), 2.80(t,J=7.2Hz,2H), 3.41-3.56(m,4H), 4.49(s,2H), 7.02(s,1H), 7.22-7.36(m,5H), 7.40(t,J=8.0Hz,1H), 7.53(t,J=8.0Hz,1H), 7.64(d,J=8.0Hz,2H), 8.01(d,J=8.0Hz,2H).

MS(FAB) m/z 404$(M+H)^{+}$.

The resulting free compound was convereted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 1.14 g of the title compound as a yellow amorphous.

Example 2 Synthesis of 1-(1-methylpiperazin-4-yl)-3-(4-methoxyphenyl)isoquinoline



1-Chloro-3-(4-methoxyphenyl)isoquinoline (526 mg) and 1-methylpiperazine (4.4 ml) were stirred at 120 °C overnight. The reaction mixture was evaporated, aqueous solution of saturated sodium bicarbonate was added thereto, followed by extracting with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by silica gel column chromatography (methylene chloride/methanol system). The resulting product was

converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol, to give the hydrochloride of the title compound as pale yellow crystals (320 mg, yield; 40%).

Hydrochloride:

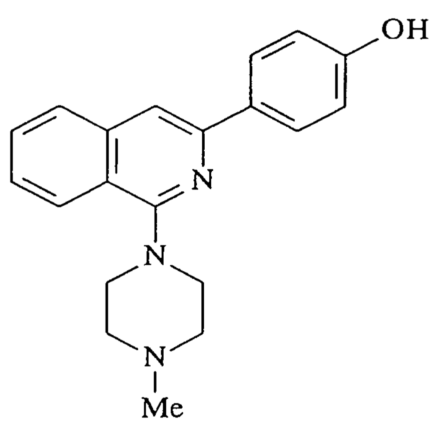
m.p.; 134-136℃

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 2.86(3H,d,J=4.4Hz), 3.26-3.44(4H,m), 3.54(2H,d,J=11.6Hz), 3.80(3H,s), 3.97(2H,d,J=11.6Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8.2Hz,6.8Hz,1.2Hz), 7.70(1H,ddd,J=8.2Hz,6.8Hz,1.2Hz), 7.93(1H,d,J=8.4Hz), 7.98(1H,s), 8.06(1H,d,J=8.4Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 334($MH^+$).

Example 3 Synthesis of 1-(1-methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline

(3-1) 1-(1-Methylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline

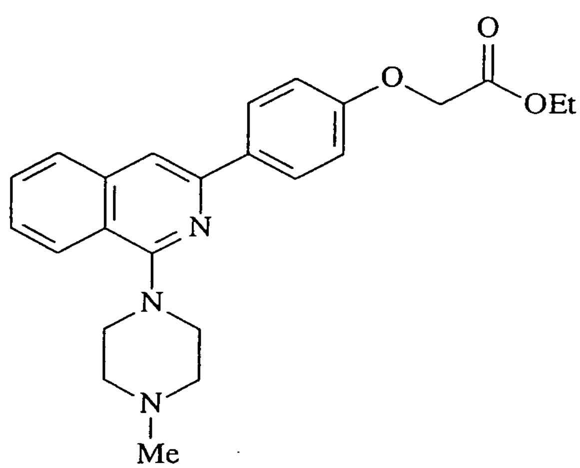


To 1-(1-methylpiperazin-4-yl)-3-(4-methoxy-1-phenyl)isoquinoline (2.07 g) was added 47% hydrobromic acid (28 ml), and the resulting mixture was heated under reflux for 6.5

hr. After the resulting solution was left for cooling, it was basified (pH=10) by adding 5N sodium hydroxide thereto, and then extracted with chloroform. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. Methanol was added thereto, and the insoluble matter was collected by filtration and dried, to give the title compound as a pale red solid (946 mg, yield; 50%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.28(3H,s), 2.60(4H,br-s), 3.40(4H,br-s), 6.85(2H,d,J=8.8Hz), 7.48(1H,dd,J=8Hz,7Hz), 7.63(1H,dd,J=8Hz,7Hz), 7.79(1H,s), 7.86(1H,d,J=8Hz), 8.00(1H,d,J=8Hz), 8.01(2H,d,J=8.8Hz), 9.62(1H,s).

<u>(3-2) 1-(1-Methylpiperazin-4-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline</u>

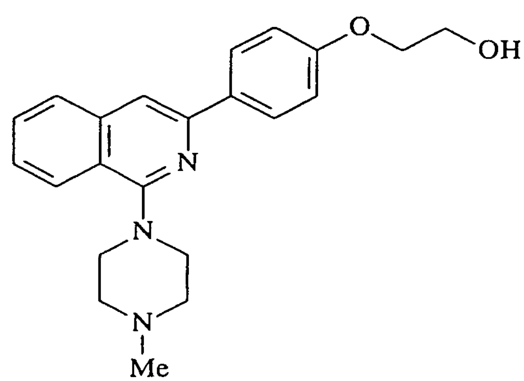



1-(1-Methylpiperazin-4-yl)-3-(4-hydroxy-1-phenyl)isoquinoline (320 mg) was dissolved in N,N-dimethylformamide (5 ml), to which was then added 60% sodium hydride (48 mg) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hr. It was ice-cooled again,

to which was then added ethyl 2-bromoacetate (166 ml), for agitation for 6 hours. The reaction mixture was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a pale yellow oil (171 mg, yield; 40 %).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 2.41(3H,s), 2.71(4H,t,J=4.4Hz), 3.56(4H,t,J=4.4Hz), 4.28(2H,q,J=7.2Hz), 4.67(2H,s), 7.01(2H,d,J=8.8Hz), 7.43(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.60(1H,s), 7.75(1H,d,8Hz), 8.04(1H,d,J=8Hz), 8.11(2H,d,8.8Hz).

(3-3) 1-(1-Methylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline




1-(1-Methylpiperazin-4-yl)-3-[4-(ethoxycarbonylmethoxy)phenyl]isoquinoline (320 mg) was dissolved in tetrahydrofuran (5 ml), to which was added lithium aluminium hydride (16 mg) under ice-cooling, followed by stirring for 5 min. To the resulting reaction mixture were then added water (16 ml), 5N sodium hydroxide (16 ml) and water (48

ml) in this order. After diluting with ethyl acetate, it was filtered through Celite and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), which was converted into a hydrochloride in a conventional manner, and then recrystallized from in ethanol, to give the hydrochloride of the title compound as yellow crystals (105 mg, yield; 50 %).

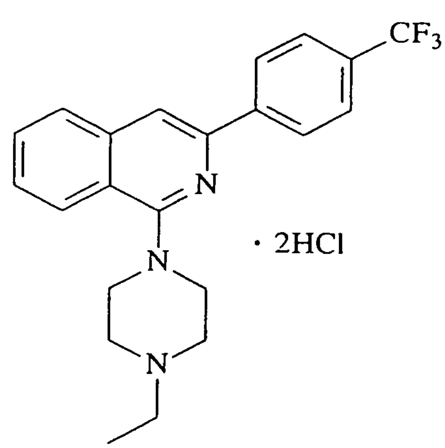
Hydrochloride:

m.p.; 131-133°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 2.85(3H,d,J=4.4Hz), 3.36(1H,t,J=11Hz), 3.38(1H,t,J=11Hz), 3.42(1H,t,J=12.6Hz), 3.45(1H,t,J=12.6Hz), 3.54(2H,d,J=11Hz), 3.73(2H,t,J=5Hz), 3.96(1H,d,J=12.6Hz), 4.04(2H,t,J=5Hz), 7.05(2H,d,J=8.8Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 7.97(1H,s), 8.06(1H,d,J=8Hz), 8.12(2H,d,J=8.8Hz), 10.95(1H,br-s).

ESI-Mass; 364($MH^+$).

Example 4 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-trifluoromethylphenyl)isoquinoline dihydrochloride



3-(4-Trifluoromethylphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.0 g) and 4-trifluoromethylbenzonitrile (1.15 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 110°C for 3 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(4-trifluoromethylphenyl)isoquinoline was reacted with N-ethylpiperazine (10 ml) at 120°C for 5 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.6Hz,3H), 2.57(q,J=7.6Hz,2H), 2.78(m,4H), 3.60(m,4H), 7.50(br-t,1H), 7.62(br-t,1H), 7.71(d,J=8.4Hz,2H), 7.74(s,1H), 7.81(d,J=8.4Hz,1H), 8.09(br-d,1H), 8.26(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized

from ethanol/ether, to give 0.19 g of the title compound as a yellow powder.

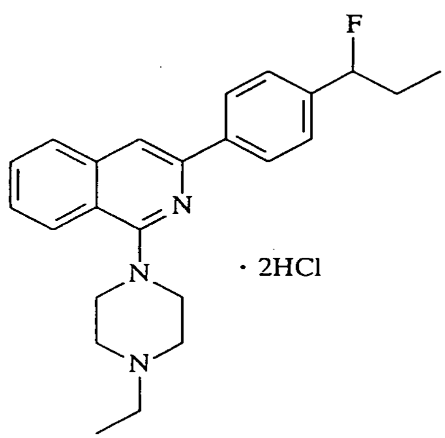
Hydrochloride:

m.p.; 131-133°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.27(m,2H), 3.30-3.41(m,2H), 3.52-3.65(m,4H), 4.02(br-d,2H), 7.67(ddd,J=8.4,7.2,1.2Hz,2H), 7.79(ddd,J=7.6,7.2,0.8Hz,1H), 7.88(d,J=8.4Hz,1H), 8.04(d,J=7.6Hz,1H), 8.16(d,J=8.4Hz,1H), 8.25(s,2H), 8.16(d,J=8.4Hz,1H), 11.27(br-s,1H).

MS(FAB) m/z 416(M+H)$^+$.

Example 5 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-fluoropropyl)phenyl]isoquinoline hydrochloride



Diethylaminosulfur trifluoride (0.27 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline (0.53 g) obtained in Example 19 in methylene chloride (30 ml) at -78 °C. After stirring the resulting mixture for 1 hr, it was returned to room temperature. An aqueous solution of saturated sodium bicarbonate and ethyl acetate were added to the resulting

reaction solution, for partitioning. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) (0.38 g), and was then converted into a hydrochloride in a conventional manner, to give 0.36 g of the title compound as a yellow powder.

Free compound:

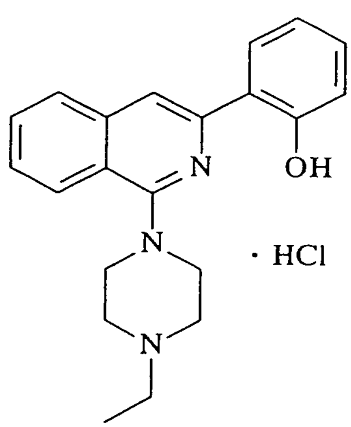
$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.01(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.82-2.10(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(m,4H), 3.59(m,4H), 5.35-5.50(m,1H), 7.42(t,J=8.0Hz,2H), 7.45(t,J=8.0Hz,1H), 7.58(t,J=8.0Hz,2H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,2H).

Hydrochloride:

m.p.; 147-149°C

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 6 Synethesis of 1-(4-ethylpiperazin-1-yl)-3-(2-hydroxyphenyl)isoquinoline</u>




1-(4-Ethylpiperazin-1-yl)-3-(2-methoxyphenyl)isoquinoline (0.38 g) obtained in Example 8 was

dissolved in 48 % hydrobromic acid (15 ml) and reacted at 120°C for 1.5 hr. The reaction solution was evaporated to a final half volume, and then ice-cooled. The resulting precipitates were collected by filtration and washed with a small amount of ice-cold water. The resulting precipitates were treated with a 2N aqueous solutiong of sodium hydroxide. The resulting precipitates were collected by filtration, and washed with water and ether/n-hexane, to give 0.23 g of the free compound of the title compound. 70 mg of the free compound was converted into a hydrochloride in a conventional manner, to give 71 mg of the hydrochloride of the title compound title compound as a yellow powder.

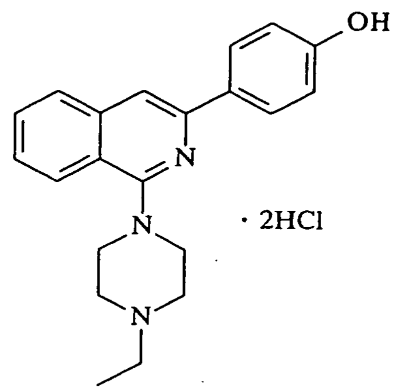
Hydrochloride:

m.p.; 228-230℃

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(t,J=7.2Hz,3H), 3.20-3.30(m,2H), 3.36-3.52(m,4H), 3.63-3.70(m,2H), 3.90-4.08(m,2H), 6.95(d,J=8.0Hz,2H), 6.95(t,J=8.0Hz,1H), 7.65(t,J=8.0Hz,2H), 7.80(t,J=8.0Hz,2H), 8.00-8.09(m,2H), 8.15(d,J=8.0Hz,2H), 8.27(s,1H).

MS(FAB) m/z 334(M+H)$^+$.

Example 7 Synethesis of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline



1-(4-Ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline (1.50 g) obtained in Example 10 was dissolved in 48 % hydrobromic acid (15 ml) and reacted at 120°C for 1.5 hr. The reaction solution was evaporated to a final half volume, and ice-cooled. The resulting precipitates were collected by filtration, and then washed with a small amount of ice-cold water. The precipitates were treated with a 2N aqueous solution of sodium hydroxide, followed by collecting the precipitates by filtration, washed with water and ether/n-hexane, and then dried in warm air, to give the title compound (1.08 g, yield; 75 %).

Free compound:

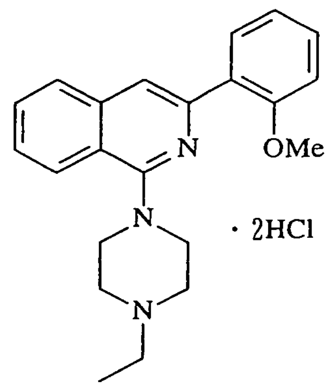
m.p.; 204-206°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.08(t,J=7.2Hz,3H), 2.38-2.52(m,2H), 2.68(br,4H), 3.42(br,4H), 6.87(d,J=8.8Hz,2H), 7.51(ddd,J=8.0,7.2,0.8Hz,1H), 6.87(ddd,J=8.0,7.2,0.8Hz,1H), 7.82(s,1H), 7.88(d,J=8.0Hz,1H), 8.02-8.06(m,1H), 8.03(d,J=8.8Hz,2H), 9.66(s,1H).

MS(FAB) m/z 334(M+H)$^+$.

<u>Example 8</u> <u>Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-</u>

methoxyphenyl)isoquinoline dihydrochloride



To 3-(2-methoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.30 g) and 2-methoxybenzonitrile (2.0 g) according to Example 10-1 was added phosphorous oxychloride (10 ml), and the resulting mixture was heated at 100 °C for 2 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water, for partitioning. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-methoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (10 ml) at 120°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^{1}$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.17(t,J=8.0Hz,3H), 2.56(q,J=8.0Hz,2H), 2.75(m,4H), 3.55(m,4H), 3.93(s,3H), 7.02(d,J=9.4Hz,1H), 7.10(t,J=9.4Hz,1H), 7.32(br-t,1H), 7.45(t,J=9.4Hz,1H), 7.58(t,J=9.2Hz,1H), 7.78(d,J=9.2Hz,1H), 7.98(s,1H), 8.08(d,J=9.2Hz,1H), 8.15(d,J=4.5Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.42 g of the title compound as a yellow powder.

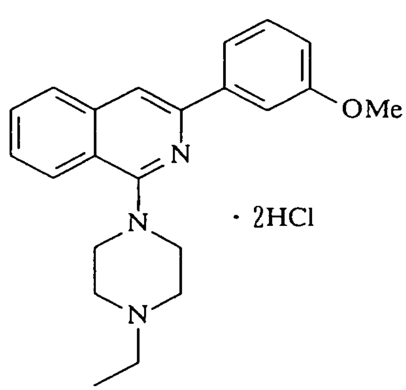
Hydrochloride:

m.p.; 133-135℃

$^{1}$H-NMR(400MHz, DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.19-3.26(m,2H), 3.29-3.41(m,2H), 3.53-3.65(m,4H), 3.90(s,3H), 3.97(br-d,2H), 7.11(br-t,1H), 7.19(d,J=8.0Hz,1H), 7.42(br-t,1H), 7.65(br-t,1H), 7.78(br-t,1H), 7.98(d,J=8.0Hz,2H), 8.06(s,1H), 8.15(d,J=8.8Hz,1H), 11.30(br-s,1H).

MS(FAB) m/z 348$(M+H)^+$.

Example 9 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(3-methoxyphenyl)isoquinoline dihydrochloride




3-(4-Methoxyphenyl)isoquinolin-1-one obtained by

reacting N-methyl-o-toluamide (1.49 g) and 3-methoxybenzonitrile (1.33 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(3-methoxyphenyl)isoquinoline. Then, it was reacted with N-ethylpiperazine (10 ml) at 120°C for 6 hr. The reaction solution was evaporated, and ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.6Hz,3H), 2.55(q,J=7.6Hz,2H), 2.76(m,4H), 3.58(m,4H), 3.90(s,3H), 6.93(dd,J=8.4,2.4Hz,1H), 7.37(t,J=8.4Hz,1H), 7.45(br-t,1H), 7.59(br-t,1H), 7.69(s,1H), 7.70-7.75(m,1H), 7.77-7.82(m,2H), 8.17(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner and recrystallized from ethanol/ether, to give 0.27 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 108-110°C

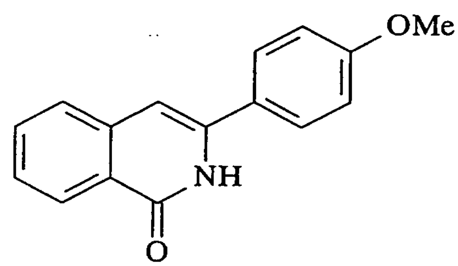
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-

3.27(m;2H), 3.35(q,J=7.2Hz,2H), 3.52-3.66(m,4H), 3.87(s,3H), 3.96-4.04(m,2H), 7.01(br-d,1H), 7.44(t,J=8.0Hz,1H), 7.63(br-t,1H), 7.73-7.82(m,3H), 8.10(d,J=8.0Hz,1H), 8.13(s,1H), 8.13(d,J=8.4Hz,1H), 11.25(br-s,1H).

MS(FAB) m/z 348$(M+H)^+$.

Example 10 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline

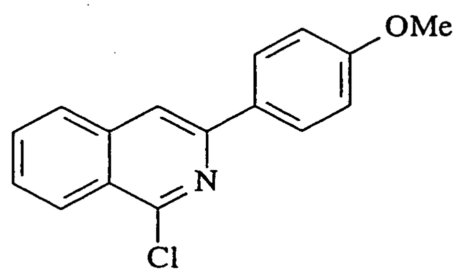
(10-1) 3-(4-Methoxyphenyl)isoquinolin-1-one



To a solution of N-methyl-o-toluamide (4.47 g) in THF (100 ml) was added dropwise 1.6 M n-BuLi (40 ml, 2.2 equivalents) in nitrogen atmosphere at 0 °C. After stirring for 2 hr, the resulting solution was cooled in a dry ice/acetone bath to -70 °C, followed by the addition of anisole (4.0 g) at once. The reaction mixture was drawn out of the dry ice/acetone bath, and then returned to room temperature. Three hours later, an aqueous solution of saturated ammonium chloride and ether were added thereto, which was stirred for further 1 hr. The resulting white precipitates were collected by filtration, and then washed with water, ether and n-hexane, in this order. The resulting precipitates were dried, to give the title compound (1.72 g, yield; 24%).

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 3.84(s,3H), 6.85(s,1H), 7.05(d,J=8.4Hz,2H), 7.46(m,1H), 7.69(s,1H), 7.65-7.72(m,1H), 7.78(d,J=8.4Hz,2H), 8.20(d,J=8.0Hz,1H).

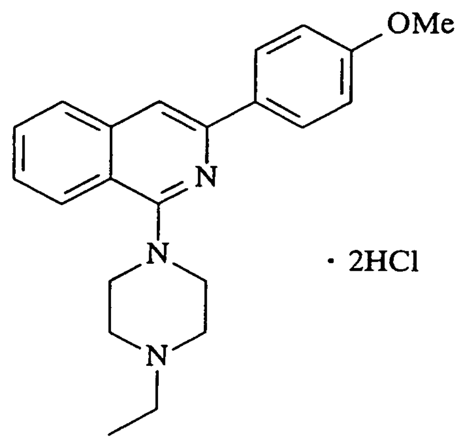
(10-2) 1-Chloro-3-(4-methoxyphenyl)isoquinoline



3-(4-Methoxyphenyl)isoquinolin-1-one (1.70 g) was added to phosphorus oxychloride (10 ml), and the resulting mixture was heated at 110 °C for 3 hr. The reaction mixture was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a white powder (1.76 g, yield; 96%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.87(s,3H), 7.02(d,J=8.4Hz,2H), 7.61(br-t,1H), 7.71(br-t,1H), 7.84(d,J=8.0Hz,1H), 7.92(s,1H), 8.07(d,J=8.4Hz,2H), 8.32(d,J=8.0Hz,1H).

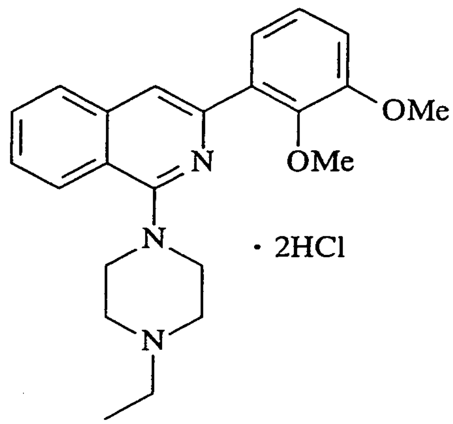
(10-3) 1-(4-Ethylpiperazin-1-yl)-3-(4-methoxyphenyl)isoquinoline



A mixture of 1-chloro-3-(4-methoxyphenyl)isoquinoline (0.89 g), N-ethylpiperazine (0.86 g) and potassium carbonate (1.10 g) was heated in dimethylformamide (20 ml) at 90°C for 12 hr. The reaction mixture was evaporated, water was added to the resulting residue, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and then the solvent was romoved. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the tilte compound as a pale brown oil (1.02 g, yield; 88%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 3.87(s,3H), 7.00(d,J=8.4Hz,2H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 11 Synthesis of 3-(2,3-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



3-(2,3-Dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.49 g) and 2,3-dimethoxybenzonitrile (1.63 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 110 °C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2,3-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 120°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.78(s,3H), 3.92(s,3H), 6.94(d,J=7.5Hz,1H), 7.16(t,J=7.5Hz,2H), 7.47(dt,J=7.6,1.2Hz,1H), 7.56-7.19(m,2H), 7.78(d,J=7.6Hz,2H), 7.96(s,1H), 8.10(d,J=7.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.19 g of the title compound as a yellow powder.

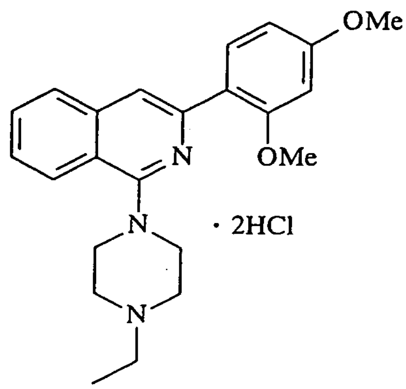
Hydrochloride:

m.p.; 122-123°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.35(q,J=7.2Hz,2H), 3.53(br-t,2H), 3.62(br-d,2H), 3.74(s,3H), 3.88(s,3H), 3.94(br-d,2H), 7.14(dd,J=8.0,1.6Hz,1H), 7.20(t,J=8.0Hz,1H), 7.49(dd,J=8.4,1.6Hz,1H), 7.65(t,J=7.2Hz,1H), 7.77(t,J=7.2Hz,1H), 7.97(s,1H), 8.00(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,1H), 11.19(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 12 Synthesis of 3-(2,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



Phosphorous oxychloride (10 ml) was added to 3-(2,4-dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.20 g) and 2,4-dimethoxybenzonitrile (2.40 g) according to Example 10-1, and the resulting mixture was heated at 100°C for 1 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2,4-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 110°C for 12 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and was then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.15(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.70(m,4H), 3.55(m,4H), 3.85(s,3H), 3.91(s,3H), 6.57(d,J=4.0Hz,1H), 6.64(dd,J=8.8,4.0Hz,1H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 7.95(s,1H), 8.04(d,J=8.0Hz,1H), 8.13(d,J=8.8Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.12 g of the title compound as a yellow powder.

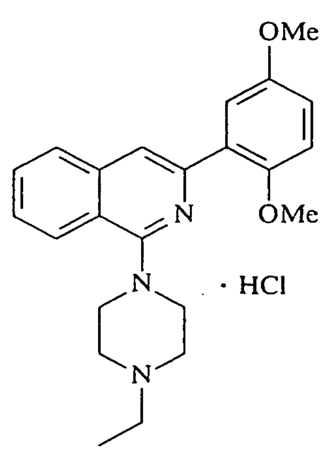
Hydrochloride:

m.p.; 145-148°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.36(t,J=7.4Hz,3H), 3.35(q,J=7.4Hz,2H), 3.44-3.55(m,2H), 3.64-3.75(m,2H), 3.77-3.88(m,2H), 3.84(s,3H), 3.86(s,3H), 4.17-4.26(m,2H), 6.66(br-s,1H), 6.67-6.82(m,1H), 7.57(dd,J=8.4,1.2Hz,1H), 7.66-7.74(m,2H), 7.88-7.84(m,2H), 8.08(br-d,1H).

MS(FAB) m/z 378(M+H)$^+$.

<u>Example 13 Synthesis of 3-(2,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride</u>



3-(2,5-Dimethoxyphenyl)isoquinolin-1-one (0.61 g) obtained by reacting N-methyl-o-toluamide (1.64 g) and 2,5-dimethoxybenzonitrile (1.80 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(2,5-dimethoxyphenyl)isoquinoline, which was then reacted with N-ethylpiperazine (15 ml) at 100°C for 8 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.86(s,3H), 3.88(s,3H), 6.88(dd,J=8.1,2.4Hz,1H), 6.96(t,J=8.1Hz,1H), 7.46(br-t,1H), 7.57(br-t,1H), 7.76-7.84(m,1H), 8.04(s,1H), 8.08(s,1H), 8.12(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.55 g of the title compound as a yellow powder.

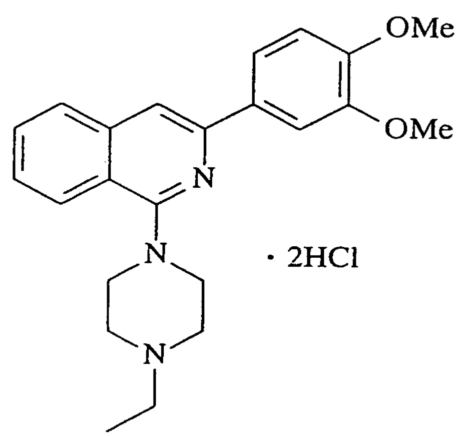
Hydrochloride:

m.p.; 189-191°C

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.36(q,J=7.2Hz,2H), 3.48(br-t,2H), 3.63(br-d,2H), 3.79(s,3H), 3.86(s,3H), 3.97(br-d,2H), 6.98(dd,J=8.0,3.2Hz,1H), 7.12(d,J=9.2Hz,1H), 7.61-7.66(m,2H), 7.51(t,J=7.2Hz,1H), 7.97(d,J=8.4Hz,1H), 8.12(s,1H), 8.11-8.16(m,1H), 10.73(br-s,1H).

MS(FAB) m/z 378(M+H)$^+$.

Example 14 Synthesis of 3-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride




3-(3,4-Dimethoxyphenyl)isoquinolin-1-one (0.98 g) obtained by reacting N-methyl-o-toluamide (2.60 g) and 3,4-dimethoxybenzonitrile (2.83 g) according to Example 10-1 was reacted with phosphorous oxychloride (15 ml) at 80°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(3,4-dimethoxyphenyl)isoquinoline was reacted with

N-ethylpiperazine (15 ml) at 100°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.78(m,4H), 3.59(m,4H), 3.95(s,3H), 4.01(s,3H), 6.98(d,J=8.4Hz,1H), 7.45(ddd,J=8.0,7.2,1.2Hz,1H), 7.58(ddd,J=8.0,7.2,1.2Hz,1H), 7.64(s,1H), 7.72(dd,J=8.4,2.0Hz,1H), 7.78(br-d,J=8.0Hz,1H), 7.84(d,J=2.0Hz,1H), 8.07(br-d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 1.38 g of the title compound as a yellow powder.

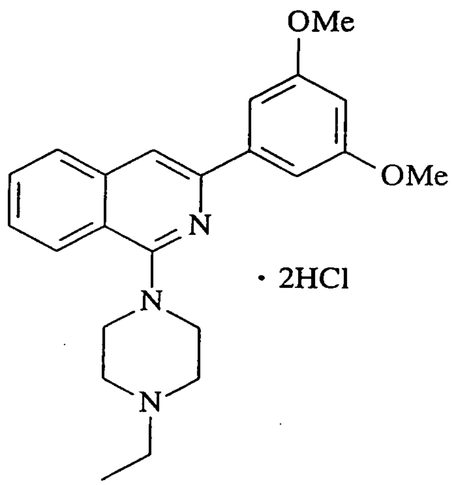
Hydrochloride:

m.p.; 125-126.5°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.6Hz,3H), 3.27(q,J=7.6Hz,2H), 3.30(br-t,2H), 3.45(br-t,2H), 3.68(br-d,2H), 3.74(s,3H), 3.78(s,3H), 3.98(br-d,2H), 6.83(d,J=8.4Hz,1H), 7.06(dd,J=8.0,2.0Hz,1H), 7.09(d,J=2.0Hz,1H), 7.29(s,1H), 7.59(br-t,1H), 7.65(br-d,1H), 7.76(br-t,2H), 7.90(br-d,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 15 Synthesis of 3-(3,5-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



3-(3,5-Dimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.49 g) and 3,5-dimethoxybenzonitrile (1.63 g) according to Example 10-1 was added to phosphorous oxychloride (10 ml), and the resulting mixture was heated at 100°C for 3 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(3,5-dimethoxyphenyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 120°C for 4 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate.

The solvent was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(m,4H), 3.58(m,4H), 3.90(s,3H), 6.51(d,J=2.4Hz,1H), 7.35(br-d,2H), 7.45(br-t,1H), 7.59(br-t,1H), 7.67(s,1H), 7.79(d,J=7.6Hz,2H), 8.07(d,J=7.6Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.51 g of the title compound as a yellow powder.

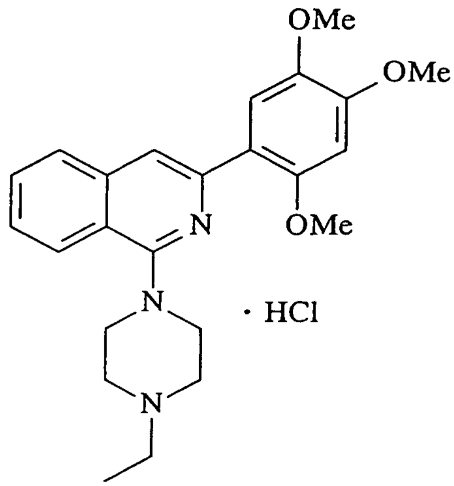
Hydrochloride:

m.p.; 121-123°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.34(q,J=7.2Hz,2H), 3.48-3.58(m,2H), 3.63(br-d,2H), 3.85(s,3H), 4.00(br-d,2H), 6.57(dd,J=2.4Hz,1H), 7.44(dx2,J=2.4Hz,2H), 7.62(br-t,1H), 7.62(br-t,1H), 8.00(br-d,1H), 8.12(br-d,1H), 8.14(s,1H), 11.02(br-s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Example 16 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2,4,5-trimethoxyphenyl)isoquinoline dihydrochloride



3-(2,4,5-Trimethoxyphenyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (1.50 g) and 2,4,5-trimethoxybenzonitrile (1.93 g) according to Example 10-1 was reacted with phosphorous oxychloride (10 ml) according to Example 10-2, to give 1-chloro-3-(2,4,5-trimethoxyphenyl)isoquinoline, which was then reacted with N-ethylpiperazine (15 ml) at 120°C for 5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was wahsed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(m,4H), 3.55(m,4H), 3.88(s,3H), 3.91(s,3H), 3.94(s,3H), 6.65(s,1H), 7.43(t,J=8.0Hz,1H),

7.56(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 7.92(s,1H), 8.03(s,1H), 8.06(d,J=8.0Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give 0.23 g of the title compound as a yellow powder.

Hydrochloride:

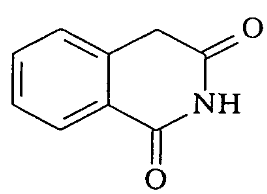
m.p.; 158-160°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.18-3.27(m,2H), 3.35(q,J=7.2Hz,2H), 3.52(br-t,2H), 3.63(br-d,2H), 3.80(s,3H), 3.88(s,3H), 3.92(s,3H), 3.99(br-d,2H), 6.84(s,1H), 7.59(br-t,1H), 7.71-7.78(m,2H), 7.76(s,1H), 7.94(d,J=8.0Hz,1H), 8.10(s,1H), 8.08-8.13(m,1H), 10.76(br-s,1H).

MS(FAB) m/z 408(M+H)$^+$.

Example 17 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline hydrochloride

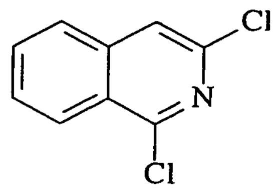
(17-1) Homophthalimide




Homophthalic anhydride (20 g) and urea (60 g) were reacted at 170°C for 1 hr. The reaction mixture was cooled, water (500 ml) was added thereto, and then the resulting precipitates were collected by filtration. The precipitate were washed with water and dried in hot air, to give 10.5 g of homophthalimide

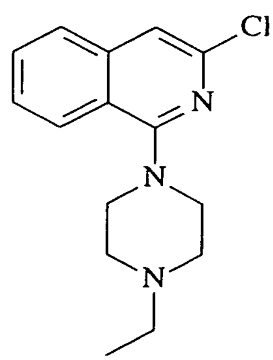
as a white powder.

(17-2) 1,3-Dichloroisoquinoline



A mixture solution of homophthalimide (10.5 g) and phenylphosphonate dichloride (30 ml) was heated at 110°C for 2 hr. After the reaction mixture was cooled, water was added thereto, and then the resulting mixture was neutralized with sodium carbonate. The resulting mixture was extracted with ethyl acetate, washed with brine, dried, and then the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride), to give 9.30 g of the title compound as white crystals.

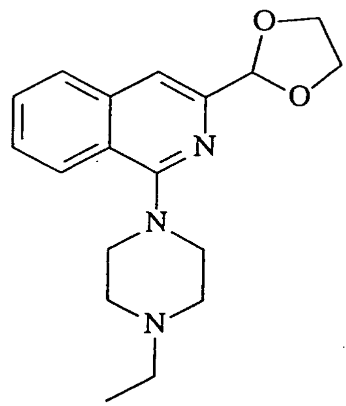
(17-3) 3-Chloro-1-(4-ethylpiperazin-1-yl)isoquinoline



1,3-Dichloroisoquinoline (9.30 g), N-ethylpiperazine (5.90 g) and potassium carbonate (10.0 g) were reacted in dimethylformamide (70 ml) at 70°C for 5 hr. The reaction solution was evaporated and partitioned between ethyl acetate and water. The resulting organic phase was washed with water,

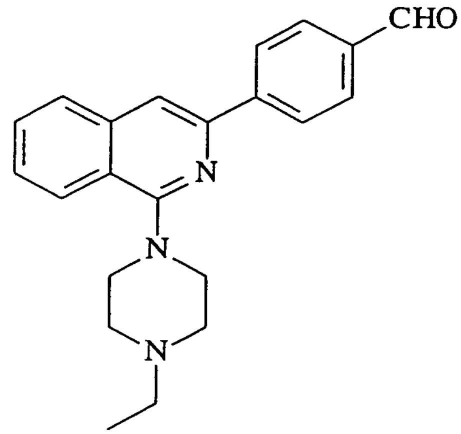
dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 12.80 g of the title compound as a pale brown oil.

(17-4) 3-[(1,3-Dioxolan-2-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



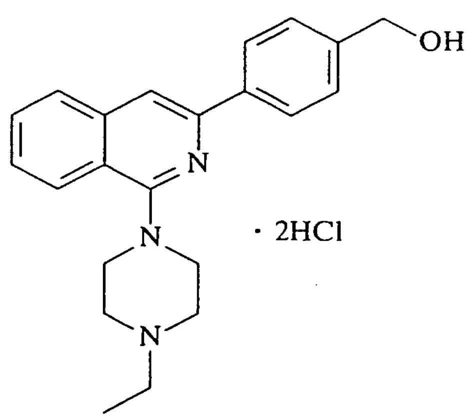
3-Chloro-1-(4-ethylpiperazin-1-yl)isoquinoline (3.5 g) and 4-(1,3,2-dioxaborynan-2-yl)-1-(1,3-dioxolan-2-yl)benzene (5.0 g) were reacted in dimethylformamide (50 ml), in the presence of cesium carbonate (7.3 g) and tetrakistriphenylphosphinepalladium (0.3 g) at 80°C in a nitrogen stream for 12 hr. The reaction solution was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 4.66 g of the title compound as a pale yellow oil.

(17-5) 1-(4-Ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline



3-[(1,3-Dioxolan-2-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (4.50 g) was dissolved in methanol (50 ml), a 1N hydrochloric acid (50 ml) was added thereto, and then the mixture was reacted at 50°C for 1 hr. The reaction solution was evaporated, basified with sodium carbonate, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine in this order, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 3.62 g of the title compound as a pale yellow oil.

(17-6) 1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxymethylphenyl)isoquinoline hydrochloride



Sodium tetrahydroboride (0.20 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (0.35g) in methanol (20 ml) at 0°C. The reaction solution was stirred for 30 min and then concentrated. Water was added to the resulting residue, and then extracted with methylene chloride. The resulting product was dried and concentrated. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate), to give the free compound of the title compound as a pale yellow oil. The free form was converted into a hydrochloride in a conventional manner, to give 0.21 g of the title compound as a yellow powder.

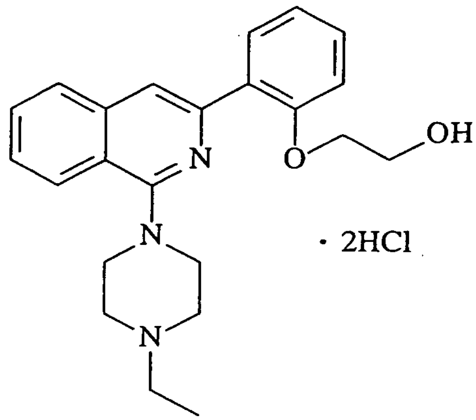
Hydrochloride:

m.p.; 145-147℃

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.17-3.27(m,2H), 3.29-3.41(m,2H), 3.50-3.66(m,4H), 3.99(d,J=9.2Hz,2H), 4.57(s,2H), 7.45(d,J=8.0Hz,2H), 7.57-7.63(m,1H), 7.71-7.77(m,1H), 7.99(d,J=8.0Hz,1H), 8.08(s,1H), 8.12(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,2H), 11.18(m,1H).

MS(FAB) m/z 348$(M+H)^+$.

<u>Example 18</u> <u>Synthesis of 3-[2-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-2-(2-benzyloxyethoxy)benzene (886 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (904 mg). Methanol (30 ml) and a palladium/carbon catalyst (200 mg) were added to the oil, which was then reacted in hydrogen atmosphere overnight at room temperature. Thereafter, the reaction solution was filtered through Celite and evaporated. The resulting residue was basified with a 1N aqueous solution of sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (733 mg, yield; 89%).

Hydrochloride:

m.p.; 158-160℃

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.32-3.42(m,2H), 3.55-3.63(m,4H), 3.79-

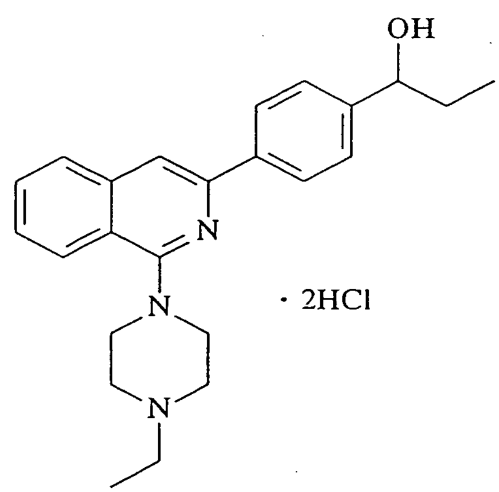
3.82(m,2H), 4.00(d,J=14.0Hz,2H), 4.14-4.16(m,2H), 7.11(t,J=8.4Hz,1H), 7.18(d,J=8.4Hz,1H), 7.39(dt,J=8.4,1.6Hz,1H), 7.64(t,J=8.0Hz,1H), 7.78(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.15(d,J=8.0Hz,1H), 8.29(s,1H).

MS(FAB) m/z 378$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.74(br,4H), 3.53(br,4H), 3.92(d,J=4.4Hz,2H), 4.21(d,J=4.4Hz,2H), 7.03(d,J=8.0Hz,1H), 7.11(dt,J=8.0,1.2Hz,1H), 7.33(dt,J=8.0,1.6Hz,1H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.75(d,J=8.0Hz,1H), 7.81(s,1H), 7.91(dd,J=8.0,1.6Hz,1H), 8.10(d,J=8.4Hz,1H).

<u>Example 19 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline hydrochloride</u>




To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (1.20 g) obtained in Example 17-5 in

tetrahydrofuran (60 ml) was added 3M ethylmagnesium bromide/diethyl ether solution (2.0 ml) at 0 °C, and the mixture was stirred for 2 hr. To the resulting reaction solution were added a 2N aqueous solution of hydrochloric acid (20 ml) and ethyl acetate. The resulting aqueous layer was basified with a 2N aqueous solution of sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1.03 g of the free compound of the title compound. 0.50 g of the resulting free compound was converted into a hydrochloride in a conventional manner, to give 0.48 g of the title compound as a yellow powder.

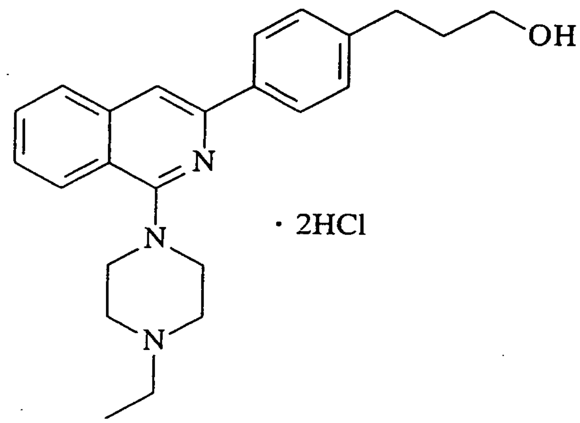
Hydrochloride:

m.p.; 143-144°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.86(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.66(m,2H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.49-3.66(m,4H), 3.95-4.04(m,2H), 4.52(t,J=6.4Hz,1H), 7.44(d,J=8.4Hz,2H), 7.58-7.64(m,1H), 7.71-7.77(m,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,2H), 11.23(m,1H).

MS(FAB) m/z 376(M+H)$^+$.

<u>Example 20 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)phenyl]isoquinoline hydrochloride</u>



[4-(2-Ethoxycarbonylethyl)phenyl]tributylstannum (2.998 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.292 g) were reacted in the presence of tetrakistriphenylphosphine (0.185 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(2-ethoxycarbonylethyl)phenyl]isoquinoline was dissolved in tetrahydrofuran (20 ml), and then added dropwise into a suspension of lithium aluminium hydride (0.106 g). The reaction solution was stirred at room temperature for 3 hr. After cooling, water and an aqueous solution of sodium hydroxide and water were added thereto in this order, and the resulting mixture was stirred at room temperature for 1 hr. The resulting precipitates were filtered off, and the residue washed with

ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.527 g of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxypropyl)phenyl]isoquinoline as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.91-1.98(m,2H), 2.56(q,J=7.2Hz,2H), 2.76-2.79(m,6H), 3.59(br-t,4H), 3.71(t,J=6.4Hz,2H), 7.31(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=7.6Hz,1H), 8.10(d,J=8.4Hz,2H).

The resulting free compound was converted into a hydrochloride in a a conventional manner, to give the title compound as a yellow powder.

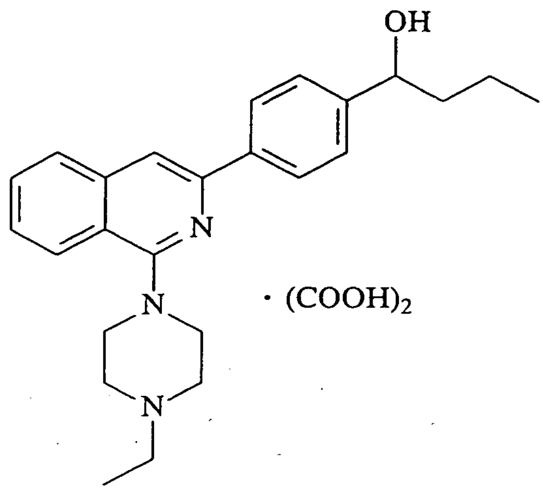
Hydrochloride:

m.p.; 116-119°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.73-1.80(m,2H), 2.68(t,J=7.8Hz,2H), 3.20-3.27(m,2H), 3.31-3.39(m,2H), 3.45(t,J=6.6Hz,2H), 3.52(br-t,2H), 3.62(br-d,2H), 4.00(br-d,2H), 7.34(d,J=8.0Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 10.95(br-s,1H).

MS(FAB) m/z 376$(M+H)^+$.

Example 21 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(1-hydroxybutyl)phenyl]isoquinoline oxalate



(4-Butyrylphenyl)tributylstannum (1.566 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.985 g) was reacted in the presence of tetrakistriphenylphosphine (0.138 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with 5N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-(4-butyrylphenyl)isoquinoline (0.177 g) was dissolved in methanol, and then excess amount of sodium borohydride in was added thereto little by little. After the completion of the reaction was confirmed, the solvent was evaporated. To the resulting residue was added water, and then extracted with ethyl acetate. The resulting product was washed with brine, dried over magnesium sulfate, and then the solvent was evaporated. The resulting residue was purified by silica gel column

chromatography (methylene chloride/methanol system), to give 0.150 g of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.95(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.31-1.62(m,2H), 1.69-1.89(m,2H), 2.57(q,J=7.2Hz,2H), 2.77(br-s,4H), 3.60(br-s,4H), 4.76(t,J=6.8Hz,1H), 7.44-7.48(m,3H), 7.59(br-t,1H), 7.70(s,1H), 7.80(d,J=7.6Hz,1H), 8.08(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

The resulting compound was converted into an oxalate in a conventional manner, to give the title compound as a white powder.

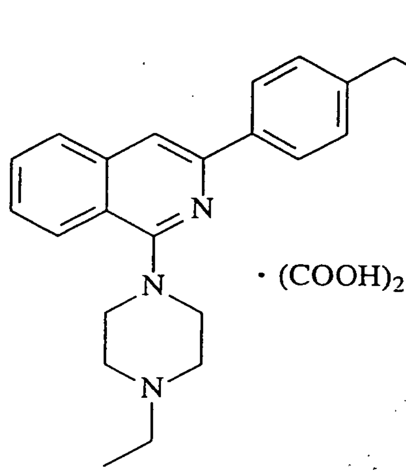
Oxalate:

m.p.; 198.5-199.5°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.89(t,J=7.2Hz,3H), 1.26(t,J=7.2Hz,3H), 1.22-1.42(m,2H), 1.53-1.69(m,2H), 3.12(br-q,2H), 3.36(br-s,4H), 3.67(br-s,4H), 4.59(t,J=6.4Hz,1H), 7.44(d,J=8.4Hz,2H), 7.60(br-t,1H), 7.73(br-t,1H), 7.98(d,J=7.6Hz,1H), 8.05(s,1H), 8.10-8.15(m,3H).

MS(FAB) m/z 390$(M+H)^+$.

Example 22 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-hydroxybutyl)phenyl]isoquinoline oxalate



[4-(3-Oxobutyl)phenyl]tributylstannum (2.457 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.405 g) were reacted in the presence of tetrakistriphenylphosphine (0.217 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with 5N sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[4-(3-ethoxycarbonylpropyl)phenyl]isoquinoline was dissolved in methanol, which was then treated with excessive sodium borohydride. The reaction solution was concentrated, extracted with ethyl acetate, washed with water and brine, dried and then the solvent was removed. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.346 g of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.25(d,J=6.4Hz,3H), 1.79-1.85(m,2H), 2.56(q,J=7.2Hz,2H), 2.70-2.86(m,6H), 3.59(br-t,4H), 3.87(tq,J=6.4Hz,1H), 7.31(d,J=8.0Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.67(s,1H), 7.78(J=8.0Hz,1H), 8.06-8.11(m,3H).

The resulting compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a white powder.

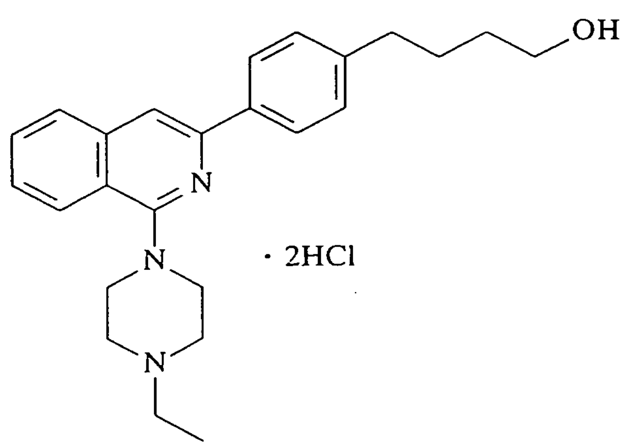
Oxalate:

m.p.; 193-194°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.10(d,J=6.0Hz,3H), 1.26(t,J=7.2Hz,3H), 1.62-1.69(m,2H), 2.60-2.77(m,2H), 3.11(br-q,2H), 3.35(br-s,4H), 3.58-3.66(m,5H), 7.33(d,J=8.4Hz,2H), 7.59(br-t,1H), 7.73(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.4Hz,2H).

MS(FAB) m/z 390(M+H)$^+$.

Example 23 Synthesis of 3-[4-(4-hydroxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 20, an oil was obtained from 1-bromo-4-(4-acetoxybutyl)benzene (1.57 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). Methanol (15 ml) and a 1N aqueous solution of sodium hydroxide (4 ml) were added thereto, and the mixture was refluxed for 3 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (656 mg, yield; 66%).

Hydrochloride:

m.p.; 140-144°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.45-1.49(m,2H), 1.63-1.70(m,2H), 2.51(br,2H), 2.65(t,J=7.2Hz,2H), 3.18-3.28(m,2H), 3.30-3.38(m,2H), 3.54(t,J=13.2Hz,2H), 3.62(d,J=10.8Hz,2H), 3.98(d,J=12.4Hz,2H), 7.33(d,J=8.4Hz,2H), 7.59(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.05(s,1H), 8.11(d,J=8.4Hz,2H), 8.12(d,J=8.0Hz,1H).

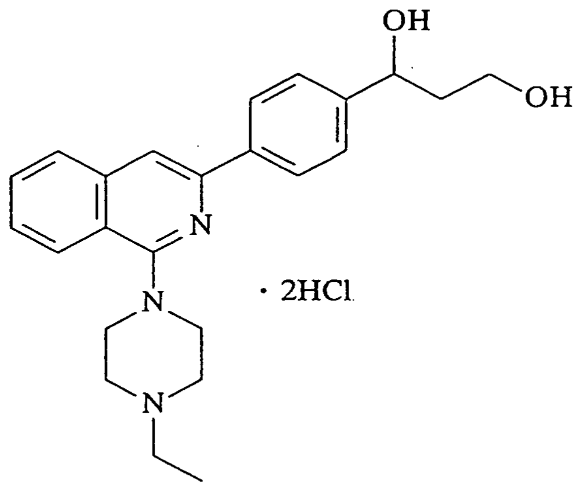
MS(FAB) m/z 390$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.61-1.77(m,4H), 2.56(q,J=7.2Hz,2H), 2.71(t,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 3.68(t,J=6.4Hz,2H), 7.28(d,J=8.4Hz,2H), 7.45(dt,J=8.0,1.2Hz,1H),

7.58(dt,J=8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,2H).

Example 24 Synthesis of 3-[4-(1,3-dihydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(1,3-isopropylidenepropyl)benzene (2.21 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (700 mg). Tetrahydrofuran (15 ml) and 1N hydrochloric acid (2 ml) were added thereto, and the resulting mixture was reacted at room temperature for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. It was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (387 mg, yield; 44%).

Hydrochloride:

m.p.; 145-147°C

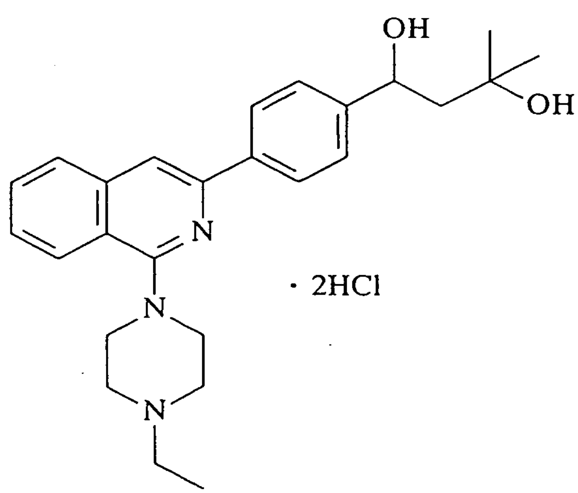
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.70-1.84(m,2H), 3.18-3.26(m,2H), 3.32-3.39(m,2H), 3.45-3.58(m,4H), 3.62(d,J=6.8Hz,2H), 4.00(d,J=13.2Hz,2H), 4.72-4.75(m,1H), 7.46(d,J=8.4Hz,2H), 7.61(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.12(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H).

MS(FAB) m/z 392(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.07(t,J=7.2Hz,3H), 1.70-1.90(m,2H), 2.45(q,J=7.2Hz,2H), 2.67(br,4H), 3.35-3.60(m,2H), 3.44(br,4H), 4.61(t,J=4.8Hz,1H), 4.73-4.75(m,1H), 5.20(d,J=4.8Hz,1H), 7.44(d,J=8.4Hz,2H), 7.55(t,J=8.0Hz,1H), 7.69(t,J=8.0Hz,1H), 7.93(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 25 Synthesis of 3-[4-(1,3-dihydroxy-3-methylbutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(1,3-isopropylidene-3-methyl-butyl)benzene (1.87 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (413 mg). Tetrahydrofuran (10 ml) and a 1N aqueous solution of hydrochloric acid (0.5 ml) were added thereto, and the mixture was reacted at room temperature for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (289 mg, yield; 69%).

Hydrochloride:

m.p.; 190-192°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.19(s,3H), 1.26(s,3H), 1.33(t,J=7.2Hz,3H), 3.22-3.26(m,2H), 3.37(br,2H), 3.50(t,J=13.6Hz,2H), 3.63(d,J=7.2Hz,2H), 4.00(d,J=12.8Hz,2H), 4.59(br,2H), 4.94(d,J=7.2Hz,1H), 7.47(d,J=8.0Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.07-8.16(m,4H).

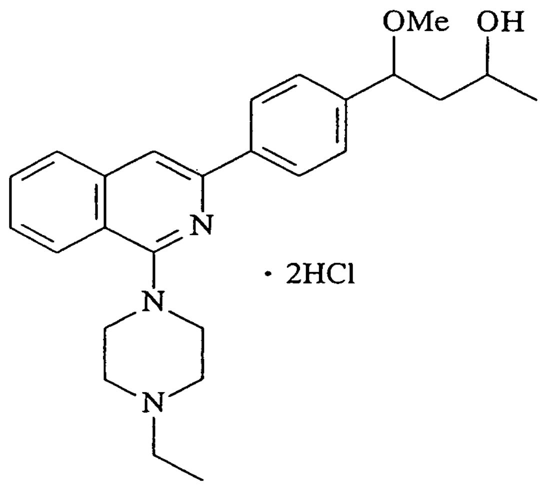
MS(FAB) m/z 420$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.08(t,J=7.2Hz,3H), 1.19(s,3H), 1.26(s,3H), 1.65-1.80(m,2H), 2.65(q,J=7.2Hz,2H), 2.67(br,4H),

3.44(br,4H), 4.74(s,1H), 4.91-4.93(m,1H), 5.41(d,J=3.2Hz,1H), 7.44(d,J=8.4Hz,2H), 7.55(d,J=8.0Hz,1H), 7.69(dt,J=8.0Hz,1H), 7.93(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(d,J=8.0Hz,1H), 8.13(d,J=8.4Hz,2H).

Example 26 Synthesis of 3-[4-(3-hydroxy-1-methoxybutyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline




In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(3-hydroxy-1-methoxybutyl)benzene (1.59 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (957 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml) were added thereto, and then the resulting mixture was refluxed for 3 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (196

mg, yield; 20%).

Hydrochloride:

m.p.; 171-174℃

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.06(t,J=6.4Hz,3H), 1.33(t,J=7.2Hz,3H), 1.52-1.60(m,1H), 1.91-1.98(m,1H), 3.12(s,3H), 3.21-3.26(m,2H), 3.34-3.39(m,2H), 3.39-3.51(m,4H), 3.63(d,J=12.0Hz,2H), 4.01(d,J=13.6Hz,2H), 4.35(t,J=6.4Hz,2H), 7.43(d,J=8.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.09(s,1H), 8.12(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,2H).

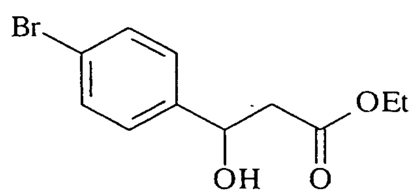
MS(FAB) m/z 420$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.71-1.76(m,1H), 1.92-2.00(m,1H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.27(s,3H), 3.60(br,4H), 3.74(br,1H), 4.06-4.10(m,2H), 4.45(dd,J=10.0,3.2Hz,1H), 7.40(d,J=8.4Hz,2H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.17(dd,J=8.4Hz,2H).

Example 27 Synthesis of 1(1-ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline

(27-1) Ethyl 3-(4-Bromophenyl)-3-hydroxypropionate

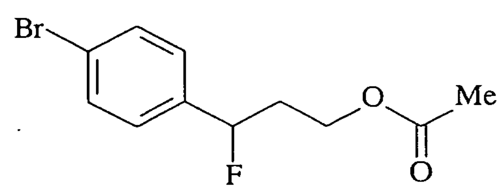


Ethyl acetate (5.8 ml) was dissolved in tetrahydrofuran

(80 ml), to which was then added 1.5M lithium diisoprypylamide/cyclohexane solution (43 ml) in nitrogen atmosphere at -70 °C, and then the mixture was stirred for 15 min. 4-Bromobenzaldehyde (10.151 g)/tetrahydrofuran (10 ml) solution was added to the reaction mixture, which was then stirred for 30 min. A saturated aqueous solution of ammonium chloride was added thereto, and then it was extracted with in ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (11.906 g, yield; 80%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.27(3H,t,J=7.2Hz), 2.68-2.71(2H,m), 3.38(1H,d,J=3.6Hz), 4.19(2H,q,J=7.2Hz), 5.07-5.12(1H,m), 7.26(2H,d,J=8.8Hz), 7.48(2H,d,J=8.8Hz).

(27-2) 3-(4-Bromophenyl)-3-fluoropropyl acetate

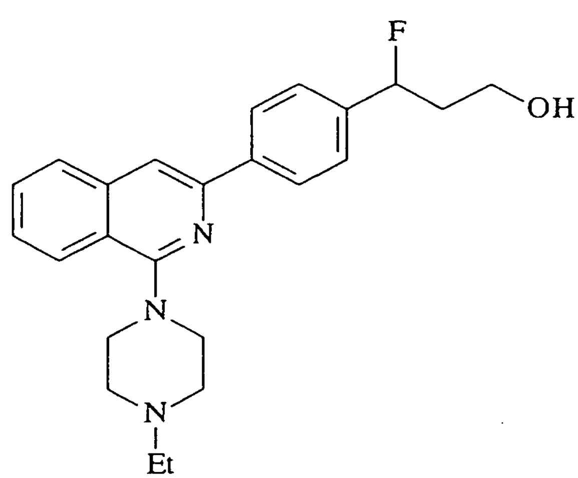



A product obtained from ethyl 3-(4-bromophenyl)-3-hydroxypropionate (7.433 g) and diethylaminosulfur trifluoride (237 ml) in the same treatment as in Example 132 was dissolved in tetrahydrofuran (60 ml). Lithium aluminium hydride (1.005 g) was added thereto under ice-cooling, and then the mixture was stirred for 20 min. To the reaction mixture were sequentially added water (1 ml), 5N sodium hydroxide (1

ml) and water (3 ml), the resulting insoluble matters were filtered off through Celite, and the resulting filtrate was evaporated. The resulting residue was dissolved in pyridine (30 ml), acetic anhydride (3.5 ml) and dimethylaminopyridine (182 mg) were added thereto, and then the mixture was stirred at room temperature for 30 min. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give 4.542 g of the title compound as a pale yellow oil (yield; 61%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.06(3H,s), 2.06-2.31(2H,m), 4.11-4.29(2H,m), 5.54(1H,ddd,J=47.6Hz,8.8Hz,4Hz), 7.22(2H,d,J=8.8Hz), 7.52(2H,d,J=8.8Hz).

(27-3) 1-(1-Ethylpiperazin-4-yl)-3-[4-(3-hydroxy-1-fluoropropyl)phenyl]isoquinoline



Acetate 3-(4-bromophenyl)-3-fluoropropane ester (833 mg)

and bis(tributyltin) (2 ml) were treated in the same manner as in Example 161-2, and then treated with 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (321 mg) in the same manner as in Example 300, to give the hydrochloride of the title compound as hygroscopic yellow crystals (187 mg, yield; 40%).

Hydrochloride:

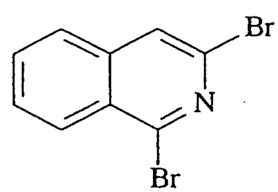
m.p.; 141-146°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 1.70-2.20(2H,m), 3.21(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.32(1H,t,J=10.4Hz), 3.35(1H,t,J=10.4Hz), 3.43-3.53(4H,m), 3.61(2H,d,J=10.4Hz), 4.08(2H,d,J=13.2Hz), 5.70(1H,ddd,J=48Hz,9.2Hz,4Hz), 7.39-7.76(4H,m), 7.95-8.24(5H,m), 10.75-10.85(1H,br-s).

ESI-Mass ; 394($MH^+$).

Example 28 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline hydrochloride

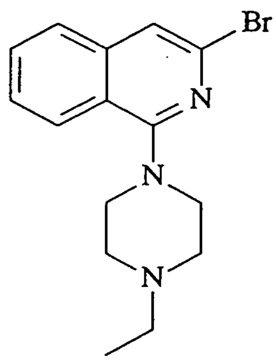
(28-1) 1,3-Dibromoisoquinoline



1,4-Dioxane (84 ml) was added to phosphorus oxybromide (23.5 g), and dissolved at room temperature. To the mixture was added homophthalimide (6.0 g) little by little, and then heated under reflux for 35 min. The reaction solution was cooled, dissolved in chloroform (300 ml) and methanol (50 ml), and evaporated. The resulting crystals were collected by

filtration, washed with 2-propanol, dried at 50°C for 1 hr, to give the title compound as pale brown crystals (6.1 g, yield; 57%).

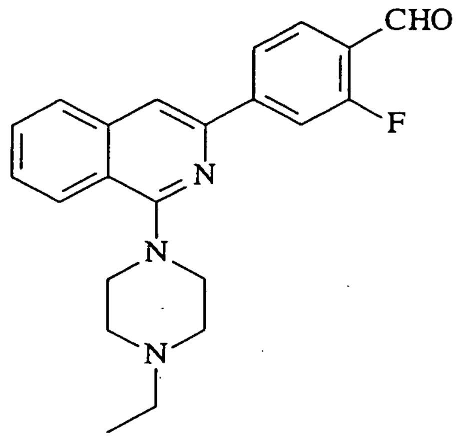
(28-2) 3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline



1,3-Dibromoisoquinoline (2.70 g), N-ethylpiperazine (1.16 g) and potassium carbonate (3.50 g) were reacted in DMF (30 ml) at 80 °C for 5 hr. The reaction solution was evaporated, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by NH silica gel column chromatography (ethyl acetate/n-hexane system), to give the title compound (2.21 g) as a pale yellow oil.

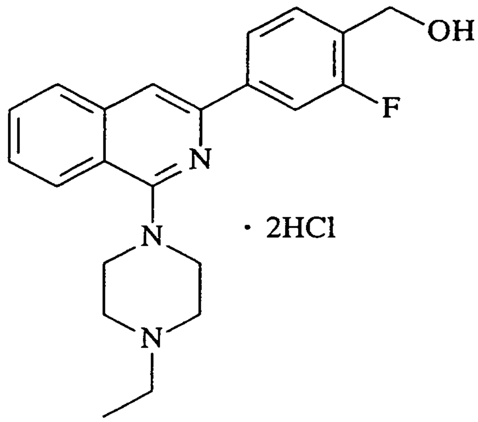
$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.66-2.73(m,4H), 3.52-3.58(m,4H), 7.40(s,1H), 7.45(dt,J=8.0,2.0Hz,1H), 7.58(dt,J=8.0,2.0Hz,1H), 7.62(dd,J=8.0,2.0Hz,1H), 7.98(dd,J=8.0,2.0Hz,1H).

(28-3) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-fluoro-4-formyl)phenyl]isoquinoline




2-Fluoro-4-tributylstannylbenzaldehyde (2.20 g) produced by heating 4-bromo-2-fluorobenzaldehyde (5.0 g) and hexabutylditin (14.3 g) in xylene (50 ml) in the presence of tetrakistriphenylphosphine (0.38 g) was reacted with 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.20 g) obtained in (28-2) in the presence of tetrakistriphenylphosphine (0.3 g) in xylene in nitrogen atmosphere for 4 hr. After cooling, the reaction solution was extracted with a 2N aqueous solution of hydrochloric acid, basified with a 5N aqueous solution of sodium hydroxide, and then reverse-extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.92 g of the title compound.

(28-4) 1-(4-Ethylpiperazin-1-yl)-3-[4-(4-hydroxymethyl-3-fluoro)phenyl]isoquinoline hydrochloride




Sodium borohydride (0.10 g) was added to a solution of 1-(4-ethylpiperazin-1-yl)-3-[4-(3-fluoro-4-formyl)phenyl]isoquinoline (0.25 g) in methanol (20 ml) at 0°C. After stirring the reaction solution for 30 min, it was concentrated. To the resulting residue was added water, which was then extracted with methylene chloride, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil. The oil was converted into a hydrochloride in a conventional manner, to give 0.15 g of the title compound as a yellow powder.

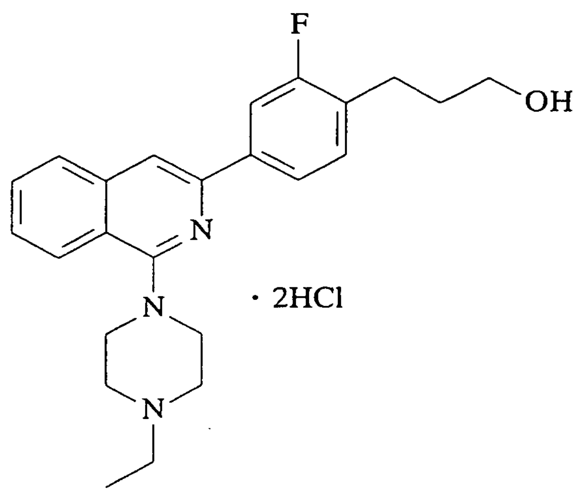
Hydrochloride:

m.p.; 228°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.35(br-q,2H), 3.49-3.67(m,4H), 4.01(br-d,2H), 4.62(s,2H), 7.57-7.67(m,1H), 7.76(br-t,1H), 7.94-8.01(m,2H), 8.05(dd,J=8.0,1.6Hz,1H), 8.13(d,J=8.4Hz,1H), 8.16(s,1H).

MS(FAB) m/z 366(M+H)$^+$.

Example 29 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline hydrochloride



Ethyl 2-fluoro-4-tributylstannylcinnamate (1.918 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.090 g) were reacted in the presence of tetrakistriphenylphosphine (0.153 g) in xylene (20 ml) in nitrogen atmosphere for 2 hr. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(2-ethoxycarbonylethen-1-yl)phenyl]isoquinoline (1.222 g) was dissolved in tetrahydrofuran (10 ml), which was then added dropwise into a suspension of lithium aluminium hydride (0.211 g). The reaction solution was heated under reflux for 8 hr, and then cooled. Then, water, an aqueous solution of sodium

hydroxide and water were added thereto in this order, and then stirred at room temperature for 1 hr. The resulting precipitates were filtered off, followed by washing with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.226 g of 1-(4-ethylpiperazin-1-yl)-3-[3-fluoro-4-(1-hydroxypropyl)phenyl]isoquinoline as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.90-1.97(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-t,4H), 2.80(t,J=7.4Hz,2H), 3.59(br-t,4H), 3.72(t,J=7.4Hz,2H), 7.16-7.19(m,1H), 7.47(br-t,1H), 7.60(br-t,1H), 7.66(s,1H), 7.79(d,J=8.4Hz,1H), 7.85-7.89(m,2H), 8.08(d,J=8.0Hz,1H).

The free compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder.

Hydrochloride:

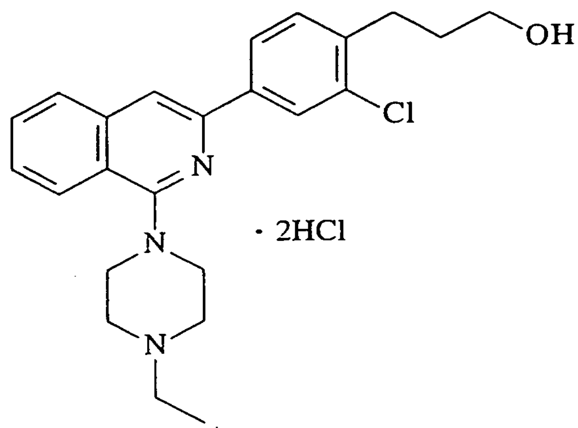
m.p.; 126-127°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 1.71-1.78(m,2H), 2.70(br-t,2H), 3.21-3.28(m,2H), 3.31-3.40(m,2H), 3.46(t,J=6.4Hz,2H), 3.48(br-t,2H), 3.64(br-d,2H), 4.02(br-d,2H), 7.42(dd,J=8.2,8.2Hz,1H), 7.63(br-t,1H), 7.76(br-t,1H), 7.93-8.00(m,3H), 8.12-8.14(m,2H).

MS(FAB) m/z 394(M+H)$^+$.

Example 30 Synthesis of 3-[3-chloro-4-(3-

hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-chloro-4-ethylpropionitebenzene (1.92 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.3 g). Under ice-cooling, tetrahydrofuran (20 ml) and lithium aluminium hydride (120 mg) were added to the oil, which was then reacted at room temperature for 1 hr. Thereafter, water (0.1 ml), a 5N aqueous solution of sodium hydroxide (0.1 ml) and water (0.3 ml) were added sequentially to the resulting reaction mixture, and the mixture was stirred at room temperature for 1 hr. The resulting residue was filtered, washed with ethyl acetate, and then purified by silica gel column chromatography, to give an oil. The oil was converted into a hydrochloride in a conventional manner, give the hydrochloride of the title compound as yellow crystals (900 mg, yield; 71%).

Hydrochloride:

m.p.; 123-124°C

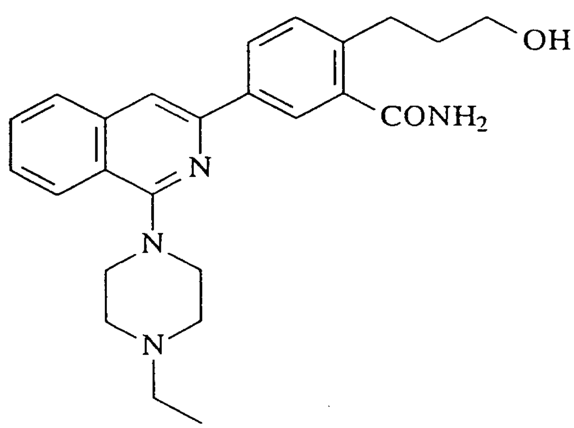
$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.72-1.82(m,2H), 2.79(t,J=7.6Hz,2H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.48(t,J=6.4Hz,4H), 3.65(d,J=11.6Hz,2H), 4.00(d,J=13.2Hz,2H), 7.47(d,J=8.0Hz,1H), 7.63(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.11(dd,J=8.0,1.6Hz,1H), 8.13(d,J=8.0Hz,1H), 8.16(s,1H), 8.22(d,J=1.6Hz,1H).

MS(FAB) m/z 410$(M+H)^+$.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.67(t,J=7.2Hz,3H), 1.90-1.97(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.88(t,J=7.6Hz,2H), 3.58(br,4H), 3.72(t,J=6.4Hz,2H), 7.32(d,J=8.0Hz,1H), 7.47(t,J=8.4Hz,1H), 7.59(t,J=8.4Hz,1H), 7.65(s,1H), 7.78(d,J=8.4Hz,1H), 7.96(dd,J=8.0,2.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.16(d,J=2.0Hz,1H).

Example 31 Synthesis of 3-[3-carboxamide-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline




In the same manners as in Examples 161-2 and then 20, an yellow oil was obtained from 1-bromo-3-carboxamide-4-(3-

acetoxypropyl)benzene (1.04 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (409 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide solution (1 ml) were added to the oil, which was then reacted at room temperature overnight. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. Then, it was recrystallized from methanol/diethyl ether, to give the title compound as white crystals (125 mg, yield; 30%).

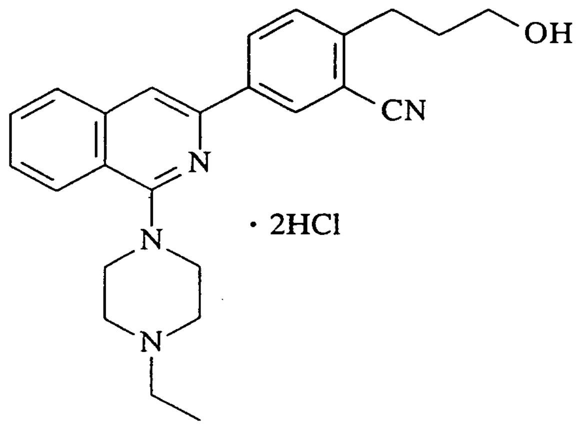
Free compound:

m.p.; 213-218°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.08(t,J=7.2Hz,3H), 1.76(tt,J=8.0,7.6Hz,2H), 2.45(q,J=7.2Hz,2H), 2.68(br,4H), 2.80(t,J=8.0Hz,2H), 3.44(br,4H), 3.39-3.44(m,2H), 4.54(t,J=5.2Hz,1H), 7.37(d,J=8.0Hz,1H), 7.45(s,1H), 7.57(t,J=8.4Hz,1H), 7.70(t,J=8.4Hz,1H), 7.90(s,1H), 7.94(d,J=8.4Hz,1H), 7.99(s,1H), 8.06(d,J=8.4Hz,1H), 8.13(s,1H), 8.14(dd,J=8.0,2.0Hz,1H).

MS(FAB) m/z 419(M+H)$^+$.

Example 32 Synthesis of 3-[3-cyano-4-(3-hydroxypropyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, a yellow oil was obtained from 5-bromo-3-carboxamide-4-(3-acetoxypropyl)benzene (1.15 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (442 mg). THF (5 ml), carbon tetrachloride (5 ml) and triphenylphosphine (588 mg) were added to the oil, and then it was reacted at 60°C for 4 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting product was extracted with 2N hydrochloric acid. The resulting aqueous layer was basified with 2N sodium hydroxide, and then reverse-extracted with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. To the resulting residue were added methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was reacted at 50°C for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with brine, dried and evaporated. Thereafter, it was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (191 mg, yield; 45%). The oil was converted into

a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$(ppm) 1.35(t,J=7.2Hz,3H), 1.78-1.85(m,2H), 2.89(t,J=8.0Hz,2H), 3.20-3.25(m,2H), 3.33-3.40(m,2H), 3.49(t,J=6.4Hz,2H), 3.55-3.65(m,4H), 4.02(d,J=13.6Hz,2H), 7.61(d,J=8.4Hz,1H), 7.65(t,J=8.4Hz,1H), 7.78(t,J=8.4Hz,1H), 7.99(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,1H), 8.22(s,1H), 8.45(dd,J=8.4,2.0Hz,1H), 8.54(d,J=2.0Hz,1H).

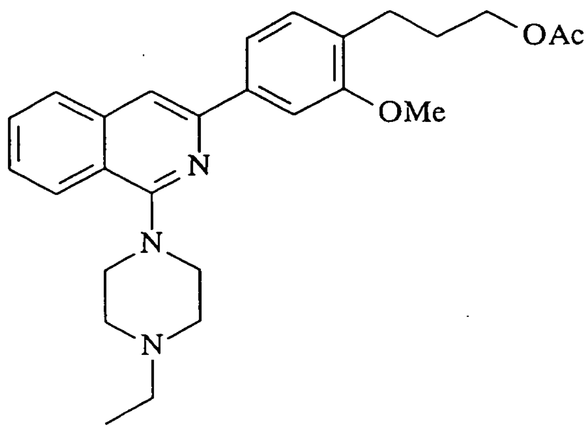
MS(FAB) m/z 401$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$(ppm) 1.20(t,J=7.2Hz,3H), 1.96-2.05(m,2H), 2.59(q,J=7.2Hz,2H), 2.79(br,4H), 3.01(t,J=7.2Hz,2H), 3.61(br,4H), 3.75(t,J=6.4Hz,2H), 7.44(d,J=8.0Hz,1H), 7.51(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.81(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.29(dd,J=8.0,1.6Hz,1H), 8.43(d,J=1.6Hz,1H).

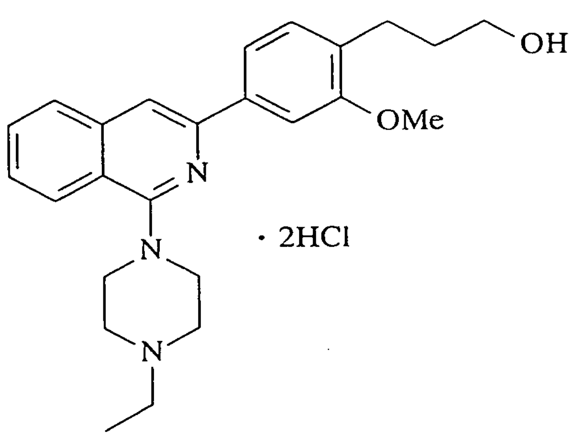
Example 33 Synthesis of 1-(4-ethylpiperazin-1-yl]-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline hydrochloride

(33-1) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-acetoxypropyl)-3-methoxyphenyl]isoquinoline



2-(3-Acetoxypropyl)-5-tributylstannylanisole (0.92 g) and 3-bromo-1-((4-ethylpiperazin-1-yl)isoquinoline (0.37 g) were reacted in the presence of tetrakistriphenylphosphine (0.3 g) in xylene in nitrogen atmosphere for 4 hr. After cooling, the reaction solution was filtered and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.28 g of the title compound.

(33-2) 1-(4-Ethylpiperazin-1-yl)-3-[4-(3-hydroxypropyl)-3-methoxyphenyl]isoquinoline hydrochloride



1-(4-Ethylpiperazin-1-yl)-3-[4-(3-acetoxypropyl)-3-

methoxyphenyl]isoquinoline was dissolved in methanol (10 ml), a 2N aqueous solution of sodium hydroxide (2 ml) was added thereto, ahd then the mixture was reacted at 50°C for 2 hr. The reaction solution was concentrated and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), which was then converted into a hydrochloride in a conventional manner to give 0.18 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 123-124℃

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.32(t,J=7.2Hz,3H), 1.66-1.76(m,2H), 2.59-2.68(m,2H), 3.20-3.29(m,2H), 3.36(br-q,2H), 3.41-3.55(m,4H), 3.64(br-d,2H), 3.93(s,3H), 4.02(br-d,2H), 7.26(d,J=8.4Hz,1H), 7.61(br-t,1H), 7.76(br-t,1H), 7.70-7.78(m,2H), 7.99(d,J=8.4Hz,1H), 8.09-8.14(m,2H).

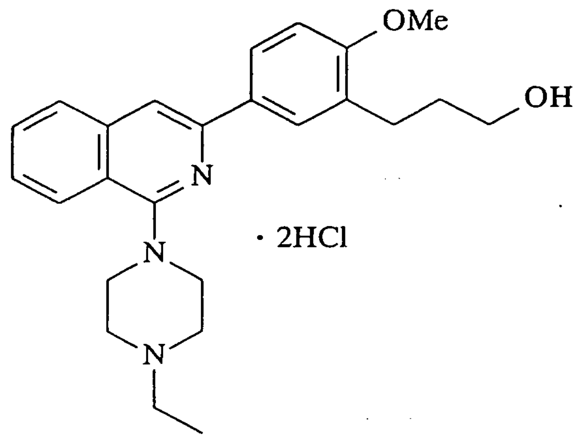
MS(FAB) m/z 406$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.84-1.92(m,2H), 2.54(q,J=7.2Hz,3H), 2.73-2.81(m,6H), 3.58(m,4H), 3.63(t,J=7.6Hz,3H), 3.96(s,3H), 7.23(d,J=6.4Hz,1H), 7.45(t,J=7.6Hz,1H), 7.57(t,J=7.6Hz,1H), 7.65(br-d,1H), 7.68(s,1H), 7.77-7.82(m,2H), 8.07(d,J=8.0Hz,1H).

Example 34 Synthesis of 3-[3-(3-hydroxypropyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline

hydrochloride



In the same manners as in Examples 161-2, and then 20, an oil was obtained from 1-bromo-3-(3-acetoxypropyl)-4-methoxybenzene (2.57 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.7 g). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (2ml) were added to the resulting oil, which was then heated under reflux for 3 hr. After cooling the reaction mixture, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil. Then, the oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (1.2 g, yield; 74%).

Hydrochloride:

m.p.; 157-160℃

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.72-1.79(m,2H), 2.67(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.32-3.39(m,2H), 3.47(t,J=6.4Hz,2H), 3.53(t,J=12.8Hz,2H),

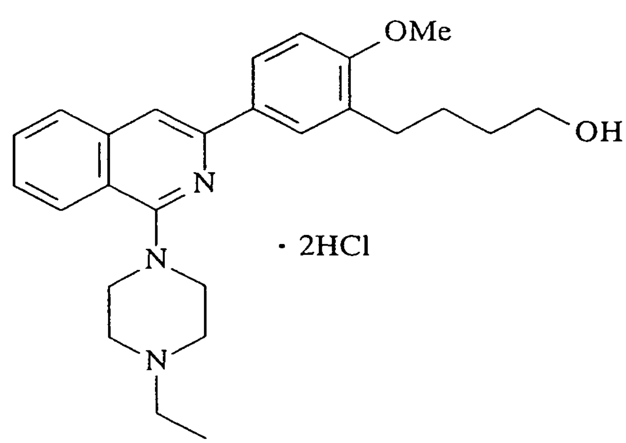
3.64(d,J=11.2Hz,2H), 3.86(s,3H), 3.99(d,J=13.2Hz,2H), 7.08(d,J=8.4Hz,1H), 7.57(t,J=8.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 7.96(d,J=2.4Hz,1H), 7.99(s,1H), 8.04(dd,J=8.4,2.4Hz,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 406$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.93(tt,J=7.2,6.4Hz,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.82(t,J=7.2Hz,2H), 3.58(br,4H), 3.66(t,J=6.4Hz,2H), 3.90(s,3H), 6.96(d,J=8.4Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 7.96(d,J=2.4Hz,1H), 8.03(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 35 Synthesis of 3-[3-(4-hydroxybutyl)-4-methoxyphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners as in Examples 161-2, and then 20, an oil was obtained from 1-bromo-3-(4-acetoxybutyl)-4-methoxybenzene (1.54 g) and 3-bromo-1-(4-ethylpiperazin-1-

yl)isoquinoline (913 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (2 ml) were added to the oil, and then reacted at at room temperature for 2 hr. Then, the reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (805 mg, yield; 90%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 128-132°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$(ppm) 1.31(t,J=7.2Hz,3H), 1.42-1.52(m,2H), 1.56-1.64(m,2H), 2.63(t,J=7.2Hz,2H), 3.16-3.24(m,2H), 3.28-3.38(m,2H), 3.41(t,J=6.4Hz,2H), 3.52(t,J=8.0Hz,2H), 3.62(d,J=11.2Hz,1H), 3.83(s,3H), 3.97(d,J=14.0Hz,1H), 7.06(d,J=8.8Hz,1H), 7.75(t,J=8.0Hz,1H), 7.70(t,J=8.0Hz,1H), 7.94(d,J=8.0Hz,1H), 7.94(d,J=2.4Hz,1H), 7.97(s,1H), 8.02(dd,J=8.8,2.4Hz,1H), 8.07(d,J=8.0Hz,1H).

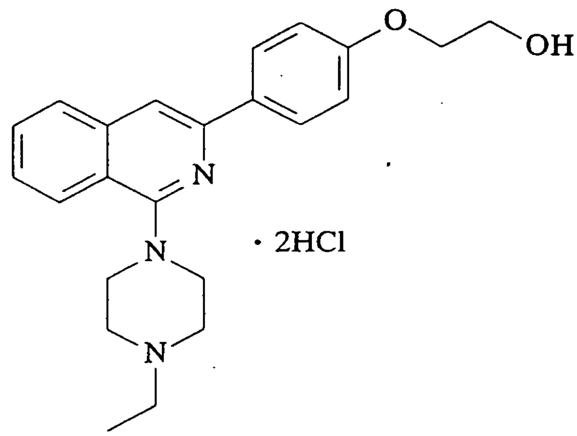
MS(FAB) m/z 420(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.67-1.74(m,4H), 2.56(q,J=7.2Hz,2H), 2.72-2.77(m,2H), 2.76(br,4H), 3.58(br,4H), 3.68-3.71(m,2H), 3.87(s,3H), 6.93(d,J=8.4Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 7.93(d,J=2.0Hz,1H),

8.00(dd,J=8.4,2.0Hz,1H), 8.05(d,J=8.4Hz,1H).

Example 36 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-hydroxyethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (1.0 g) obtained in Example 7 was dissolved in tetrahydrofuran (30 ml), followed by the addition of 60% sodium hydride (0.14 g). After the evolution of hydrogen ceased, 2-(t-butyl)dimethylsilyloxyethyl bromide (1.0 g) was added thereto, and the mixture was heated under reflux for 8 hr. The reaction solution was cooled to room temperature, and then it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. To the resulting residue was added a 2N aqueous solution of hydrochloric acid, which was then stirred at 50°C for 30 min. The reaction solution was washed with ethyl acetate. The resulting aqueous layer was basified by adding 2N sodium hydroxide thereto, and extracted with ethyl acetate. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel

column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a white powder. Then, the powder was converted into a hydrochloride in a conventional manner, to give 0.71 g of the title compound as a pale yellow powder.

Hydrochloride:

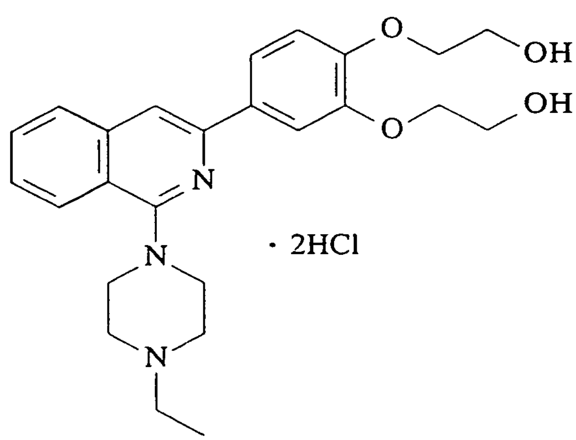
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.40(q,J=7.2Hz,2H), 3.50(br-t,2H), 3.62(br-d,2H), 3.97(br-d,2H), 6.90(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.93(s,2H), 7.91-7.96(m,1H), 8.04(d,J=8.8Hz,2H), 8.08(d,J=8.8Hz,2H), 10.92(br-s,1H).

Free compound:

m.p.; 127-129°C

MS(FAB) m/z 378(M+H)$^+$.

Example 37 Synthesis of 3-[3,4-di(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




3-[3,4-Di(2-benzyloxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (2.23 g) was obtained from 3-[3,4-di(2-benzyloxyethoxy)phenyl]-1-chloroisoquinoline

(1.97 g) obtained by the same treatment as in Example 20, potassium carbonate (2.5 g) and N-ethylpiperazine (5 ml). The resulting compound was converted into a hydrochloride, methanol (100 ml) and a palladium/carbon catalyst(50 mg) were added thereto, and then the mixture was reacted in hydrogen atmosphere at room temperature overnight. Subsequently, the reaction solution was filtered through Celite and evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then it was extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (686 mg, yield; 44%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as white crystals.

Hydrochloride:

m.p.; 130-132°C

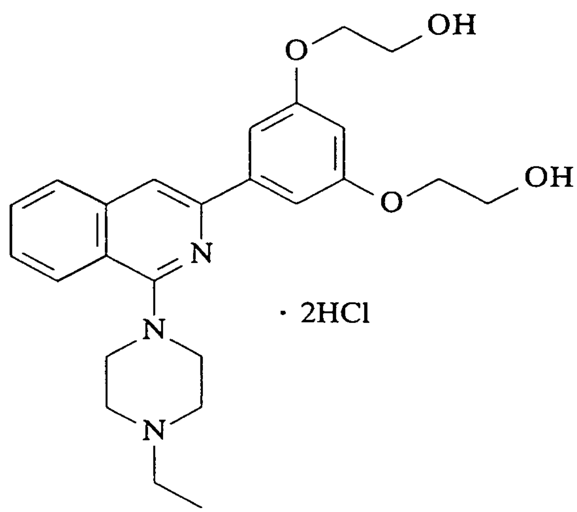
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.51(t,J=12.8Hz,2H), 3.63(d,J=11.2Hz,2H), 3.74-3.78(m,4H), 4.00(d,J=13.2Hz,2H), 4.07(t,J=5.2Hz,2H), 4.14(t,J=5.2Hz,2H), 7.11(d,J=8.4Hz,1H), 7.58(dt,J=8.0,1.2Hz,1H), 7.73(dt,J=8.0,1.2Hz,1H), 7.76(dd,J=8.4,2.4Hz,1H), 7.81(d,J=2.4Hz,1H), 7.96(d,J=8.0Hz,1H), 8.04(s,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 438(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.58(br,4H), 3.97-4.01(m,4H), 4.18-4.20(m,2H), 4.26-4.27(m,2H), 7.06(d,J=8.4Hz,1H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(s,1H), 7.78(dd,J=8.4,2.0Hz,1H), 7.79(d,J=8.0Hz,1H), 7.91(d,J=2.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 38 Synthesis of 3-[3,5-di(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



From 3-[3,5-di(2-benzyloxyethoxy)phenyl]-1-chloroisoquinoline (1.24 g) obtained by the same treatment as in Example 20, potassium carbonate (1.6 g) and N-ethylpiperazine (5 ml), 3-(3,3-dibenzyloxyethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (1.70 g) was obtained. The resulting compound was then converted into a hydrochloride, followed by the treatment with a palladium/carbon catalyst (50 mg) added, in the same manner as in Example 18, to give the free

compound of the title compound (510 mg, yield; 42%). The resulting free compound was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 232-234°C

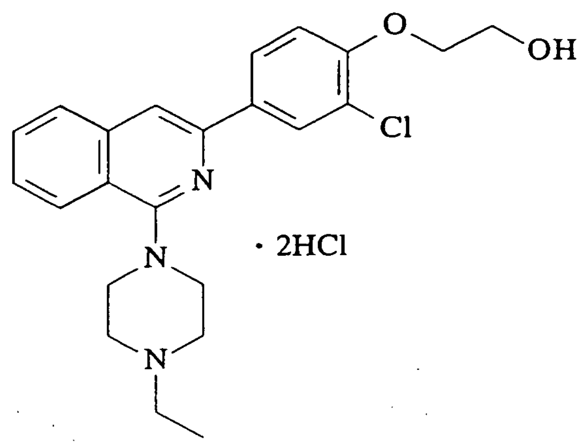
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.40(m,2H), 3.46-3.52(m,2H), 3.65(d,J=11.6Hz,2H), 3.76(t,J=5.2Hz,4H), 3.99(d,J=13.2Hz,2H), 4.09(t,J=5.2Hz,4H), 6.57(t,J=2.0Hz,1H), 7.37(s,1H), 7.38(s,1H), 7.62(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H), 8.15(s,1H).

MS(FAB) m/z 438(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.58(br,4H), 4.01(t,J=4.8Hz,4H), 4.18(t,J=4.8Hz,4H), 6.54(t,J=2.0Hz,1H), 7.40(d,J=2.0Hz,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.79(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,1H).

Example 39 Synthesis of 3-[3-chloro-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-chloro-4-(2-benzyloxyethoxy)benzene (2.52 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.3 g). Methanol (30 ml) and palladium/carbon catalyst (200 mg) were added to the oil, which was then reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (1.26 g, yield; 99 %). The oil was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 138-140°C

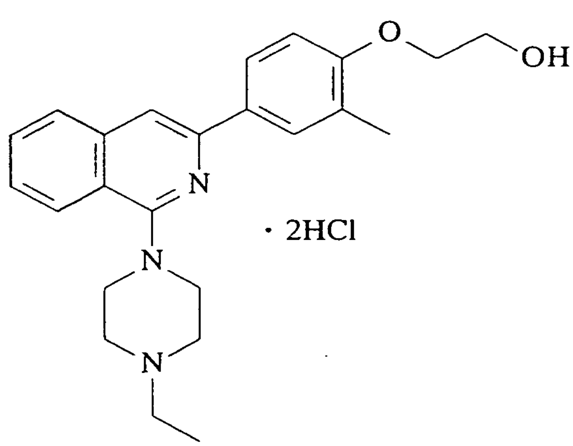
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.38(m,2H), 3.53(t,J=13.6Hz,2H), 3.64(d,J=11.6Hz,2H), 3.79(t,J=4.8Hz,2H), 3.99(d,J=13.6Hz,2H), 4.17(t,J=4.8Hz,2H), 7.30(d,J=8.8Hz,1H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.97(d,J=8.0Hz,1H), 8.09(s,1H), 8.11(d,J=8.0Hz,1H), 8.14(dd,J=8.4,2.4Hz,1H), 8.25(d,J=2.4Hz,1H).

MS(FAB) m/z 412$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 2.59(q,J=7.2Hz,2H), 2.79(br,4H), 3.61(br,4H), 4.03(t,J=4.4Hz,2H), 4.22(t,J=4.4Hz,2H), 7.04(d,J=8.8Hz,1H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.77(d,J=8.0Hz,1H), 8.03(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H), 8.19(d,J=2.4Hz,1H).

Example 40 Synthesis of 3-[3-methyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners as in Examples 161-2 and then 20, an

oil was obtained from 1-bromo-3-methyl-4-(2-benzyloxyethoxy)benzene (1.48 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (495 mg). Methanol (30 ml) and palladium/carbon catalyst (100 mg) were added thereto, and the resulting mixture was reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then partitioned between ethyl acetate and water. The resulting organic phase was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (200 mg, yield; 44%). The oil was then converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 133-136°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 2.28(s,3H), 3.18-3.28(m,2H), 3.30-3.40(m,2H), 3.50(t,J=12.0Hz,2H), 3.64(d,J=10.8Hz,2H), 3.77(t,J=4.8Hz,2H), 3.99(d,J=14.0Hz,2H), 4.07(t,J=5.2Hz,2H), 7.06(d,J=8.8Hz,1H), 7.57(t,J=8.0Hz,1H), 7.72(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 7.99-8.03(m,3H), 8.09(d,J=8.0Hz,1H).

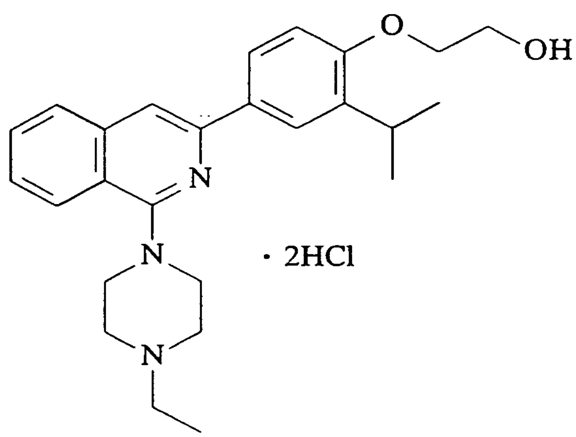
MS(FAB) m/z 392(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 2.35(s,3H),

2.58(br,2H), 2.78(br,4H), 3.61(br,4H), 4.02(t,J=4.4Hz,2H), 4.17(t,J=4.4Hz,2H), 6.93(d,J=8.4Hz,1H), 7.33(t,J=8.4Hz,1H), 7.57(t,J=8.4Hz,1H), 7.62(s,1H), 7.77(d,J=8.4Hz,1H), 7.96(br,1H), 7.99(dd,J=8.4,2.0Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 41 Synthesis of 3-[3-isopropyl-4-(2-hydroxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-3-isopropyl-4-(2-benzyloxyethoxy)benzene (3.45 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). Methanol (80 ml) and palladium/carbon catalyst (300 mg) were added thereto, which was then reacted in hydrogen atmosphere at room temperature overnight. After the reaction solution was filtered through Celite, it was evaporate. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was

purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (650 mg, yield; 40%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 248-250°C (decomp.)

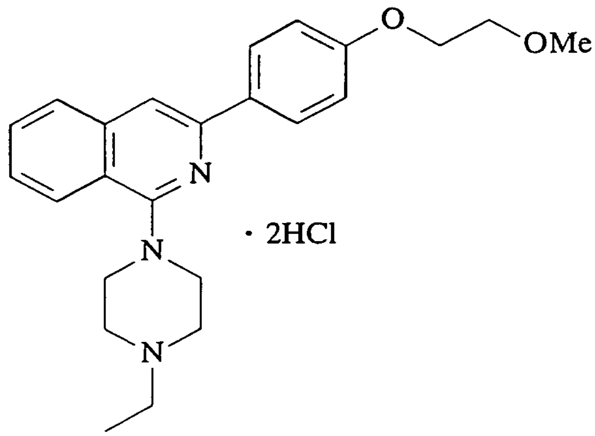
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.26(s,3H), 1.28(s,3H). 1.34(t,J=7.2Hz,3H), 3.26-3.28(m,2H), 3.30-3.39(m,3H), 3.60(t,J=8.8Hz,2H), 3.64(d,J=11.2Hz,2H), 3.78(t,J=4.8Hz,1H), 3.99(d,J=13.2Hz,2H), 4.08(t,J=4.8Hz,1H), 4.26-4.28(m,1H), 4.40-4.42(m,1H), 7.08(t,J=8.0Hz,1H), 7.57(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 7.99-8.06(m,2H), 8.00(s,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 420(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.28(d,J=7.2Hz,6H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.37-3.44(m,1H), 3.59(br,4H), 4.02(t,J=4.4Hz,2H), 4.16(t,J=4.4Hz,2H), 6.94(d,J=8.4Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(s,1H), 7.78(d,J=8.0Hz,1H), 7.97(dd,J=8.4,2.4Hz,1H), 8.06(d,J=8.4Hz,1H), 8.07(d,J=2.4Hz,1H).

Example 42 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.420 g) obtained in Example 7 was dissolved in N,N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (0.06 g). After the evolution of hydrogen was ceased, 2-methoxyethyl bromide (178 μl) was added thereto, and the mixture was stirred 50°C for 3.5 hr. After the reaction solution was cooled to room temperature, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1-(4-ethylpiperazin-1-yl)-3-[4-(2-methoxyethoxy)phenyl]isoquinoline as a white powder. The compound was converted into a hydrochloride in a conventional manner, to give 0.457 g of the title compound as a yellow powder.

Hydrochloride:

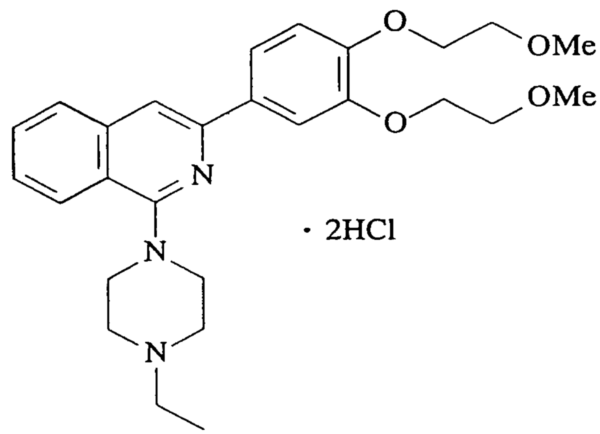
m.p.; 184.5-185°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_3$); δ (ppm) 1.33(t,J=7.2Hz,3H), 3.21-3.27(m,2H), 3.31-3.39(2H,m), 3.33(s,3H), 3.49(br-t,2H),

3.63(br-d,2H), 3.69-3.71(m,2H), 3.99(br-d,2H), 4.16-4.18(m,2H), 7.08(d,J=8.8Hz,2H), 7.56(br-t,1H), 7.72(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.00(s,1H), 8.10(d,J=8.4Hz,1H), 8.15(d,J=7.0Hz,2H), 10.74(br-s,1H).

MS(FAB) m/z 392(M+H)$^+$.

<u>Example 43</u> <u>Synthesis of 3-[3,4-di(2-methoxyethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manner as in Example 20, the free compound of the title compound was obtained (1.45 mg, yield; 95%) from 3-[3,4-di(methoxyethoxy)phenyl]-1-chloroisoquinoline (1.28 g), potassium carbonate (913 mg) and ethylpiperazine (30 ml). The compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 143-144°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.40(m,2H), 3.34(s,3H), 3.36(s,3H), 3.54-3.63(m,4H), 3.69-3.71(m,4H), 3.99(d,J=13.6Hz,2H), 4.16-

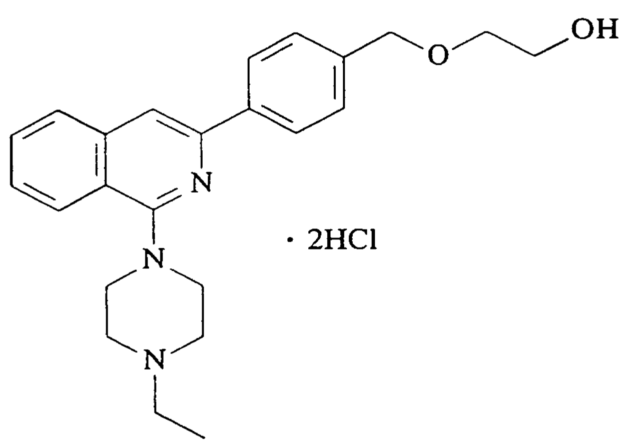
4.18(m,2H), 4.23-4.25(m,2H), 7.11(d,J=8.4Hz,1H), 7.58(dt,J=8.0,1.2Hz,1H), 7.73(td,J=8.0,1.2Hz,1H), 7.78(dd,J=8.4,2.0Hz,1H), 7.80(d,J=2.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.04(s,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 466$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.47(s,3H), 3.55(s,3H), 3.57(br,4H), 3.79-3.84(m,4H), 4.21-4.24(m,2H), 4.28-4.30(m,2H), 7.01(d,J=8.4Hz,1H), 7.43(dt,J=8.0,1.2Hz,1H), 7.56(dt,J=8.0,1.2Hz,1H), 7.61(s,1H), 7.72(dd,J=8.4,2.0Hz,1H), 7.76(d,J=8.0Hz,1H), 7.85(d,J=2.0Hz,1H), 8.06(d,J=8.0Hz,1H).

<u>Example 44 Synthesis of 3-[4-(2-hydroxyethoxy)methylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>




In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(2-benzyloxyethoxy)methylbenzene (1.72 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (854 mg). Methanol (20 ml)

and palladium/carbon catalyst (20 mg) were added thereto, which was then reacted in hydrogen atmosphere at room temperature overnight. Thereafter, the reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide, which was then extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (567 mg, yield; 73%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 129-131$^{\circ}$C

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.33-3.39(m,2H), 3.55-3.64(m,8H), 4.00(d,J=13.6Hz,2H), 4.57(s,2H), 7.48(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.10(s,1H), 8.12(d,J=8.0Hz,1H), 8.19(d,J=8.4Hz,2H).

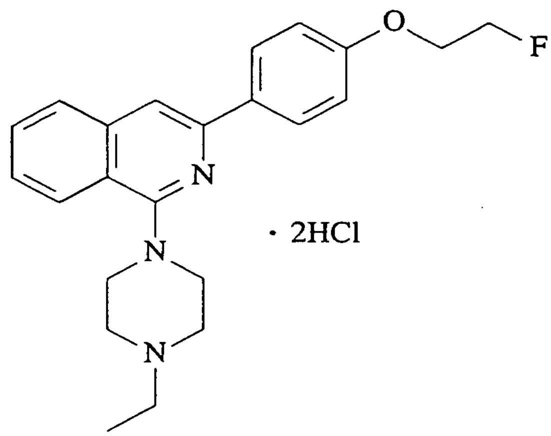
MS(FAB) m/z 392(M+H)$^{+}$.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.60(br,4H), 3.64(t,J=4.8Hz,2H), 3.79(t,J=4.4Hz,2H), 4.63(s,2H), 7.44(d,J=8.4Hz,2H), 7.47(dt,J=8.4,1.2Hz,1H), 7.59(dt,J=8.4,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.4Hz,1H),

8.08(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H).

Example 45 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline dihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.514 g) obtained in Example 7 was dissolved in N, N-dimethylformamide (5 ml), followed by the addition of 60% sodium hydride (0.075 g). After the evolution of hydrogen was ceased, 2-fluoroethyl bromide (230 μl) was added thereto, and then heated under reflux for 8 hr. After the reaction solution was cooled to room temperature, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.582 g of 1-(4-ethylpiperazin-1-yl)-3-[4-(2-fluoroethoxy)phenyl]isoquinoline as a white powder. The compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder.

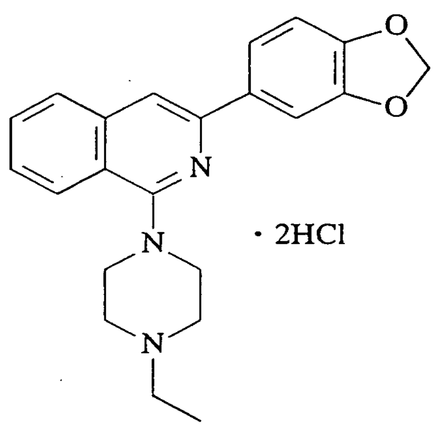
Hydrochloride:

m.p.; 223-224°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.4Hz,3H), 3.21-3.27(m,2H), 3.31-3.39(m,2H), 3.50(br-t,2H), 3.63(br-d,2H), 3.99(br-d,2H), 4.41(dt,J=4.0,30.0Hz,2H), 4.79(dt,J=4.0,48.0Hz,2H), 7.11(d,J=8.8Hz,2H), 7.58(br-t,1H), 7.73(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.4Hz,1H); 8.16(d,J=8.8Hz,2H), 10.77(br-s,1H).

MS(FAB) m/z 380(M+H)$^+$.

Example 46 Synthesis of 3-(3,4-methylenedioxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



The free compound of the title compound was obtained (425 mg, yield; 94%) from 3-(3,4-methylenedioxyphenyl)-1-chloroisoquinoline (356 mg) and ethylpiperazine (10 ml) in the same manner as in Example 2. The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.30-3.38(m,2H), 3.52(t,J=12.0Hz,2H),

3.62(d,J=11.2Hz,2H), 3.99(d,J=13.2Hz,2H), 6.10(s,2H), 7.06(d,J=8.0Hz,1H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.75(d,J=2.0Hz,1H), 7.77(dd,J=8.0,2.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.01(s,1H), 8.09(d,J=8.0Hz,1H).

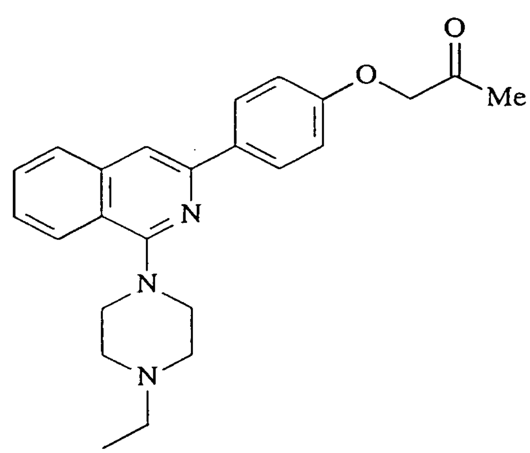
MS(FAB) m/z 362$(M+H)^+$.

m.p.; 223-227°C

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.58(br,4H), 6.02(s,2H), 6.91(d,J=8.4Hz,2H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(s,1H), 7.69(dd,J=8.4,1.6Hz,1H), 7.71(br,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 47 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-acetonyloxyphenyl)isoquinoline

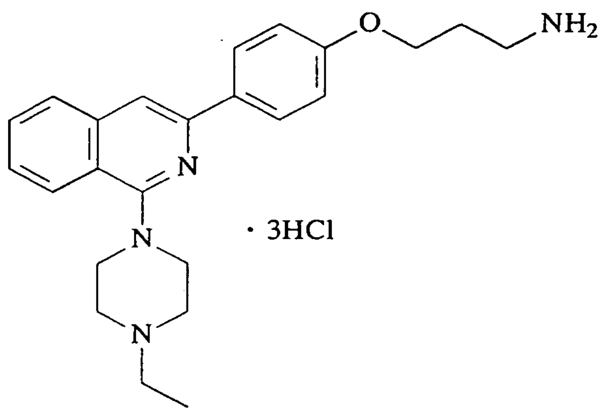



The title compound was obtained (346 mg, yield; 80%) as a yellow oil from 1-(1-ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (319 mg) and 1-bromo-2-propanone (100 mg), in the same manner as in Example 49.

$^1H$-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 2.31(3H,s), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 3.58(4H,t,J=4.4Hz), 4.59(2H,s), 6.98(2H,d,J=8.8Hz), 7.45(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,s), 7.76(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 8.13(2H,d,J=8.8Hz).

ESI-Mass; 390($MH^+$).

Example 48 Synthesis of 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




Hydrazine monohydrate (0.16 ml) and ethanol (5 ml) were added to 3-[4-(3-phthalimidepropyloxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (182 mg), and the resulting mixture was heated under reflux for 4 hr. Thereafter, the reaction solution was partitioned between chloroform and water. The resulting organic layer was washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a yellow oil (482 mg, yield; 48%). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 173-176°C

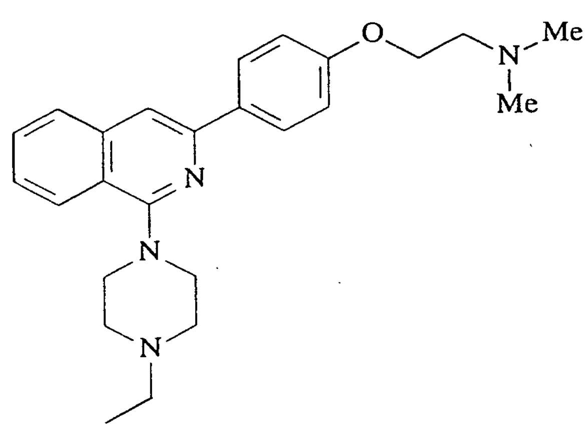
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.04-2.12(m,2H), 2.94-3.00(m,2H), 3.18-3.26(m,2H), 3.32-3.38(m,2H), 3.52-3.63(m,4H), 3.97(d,J=12.8Hz,2H), 4.16(t,J=6.4Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.13(br,2H), 8.17(d,J=8.8Hz,2H).

MS(FAB) m/z 391(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.04(s,2H), 2.12-2.18(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.42(t,J=6.4Hz,2H), 3.58(br,4H), 4.12(t,J=6.0Hz,2H), 7.00(d,J=8.8Hz,2H), 7.43(t,J=8.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.10(d,J=8.8Hz,2H).

<u>Example 49 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-dimethylaminoethoxy)phenyl]isoquinoline</u>



1-(1-Ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (500 mg) was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of 60% sodium hydride (144 mg) under ice-cooling, and the resulting mixture was stirred at room temperature for 45 min. After the reaction solution was ice-cooled again, 2-dimethylaminomethyl chloride hydrochloride (259 mg) was added thereto, and the mixture was stirred at room temperature for overnight. The reaction mixture was thereafter partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The residue was purified by (NH) silica gel column chromatography (methylene chloride/methanol system), and the resulting product was converted into a hydrochloride in a conventional manner and recrystallized from hydrous ethanol/ether, to give the hydrochloride of the title compound as yellow crystals (595 mg, yield; 80%).

Hydrochloride:

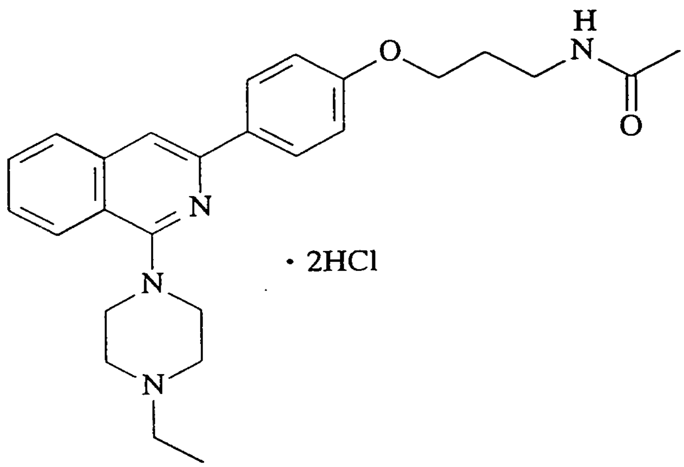
m.p.; 153-158°C

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.32(3H,t,J=7.2Hz), 2.83(3H,s), 2.84(3H,s), 3.19(2H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.30(1H,t,J=13.6Hz), 3.33(1H,t,J=13.6Hz), 3.51(1H,t,J=5.2Hz), 3.48-3.51(1H,m), 3.59(2H,d,J=13.6Hz), 3.95(2H,d,J=13.6Hz), 4.43(2H,t,J=5.2Hz), 7.13(2H,d,J=8.8Hz), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.94(1H,d,J=8Hz), 8.08(1H,d,J=8Hz), 8.17(2H,d,J=8.8Hz),

10.70(1H,br-s), 11.32(1H,br-s).

ESI-Mass; 405($MH^+$).

Example 50 Synthesis of 3-[4-(3-acetamidepropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



Acetic anhydride (0.06 ml), pyridine (0.07 ml) and THF (4 ml) were added to 3-[4-(3-aminopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (182 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was thereafter partitioned between ethyl acetate and water. The resulting organic phase was washed with brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (8 mg, yield; 4%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

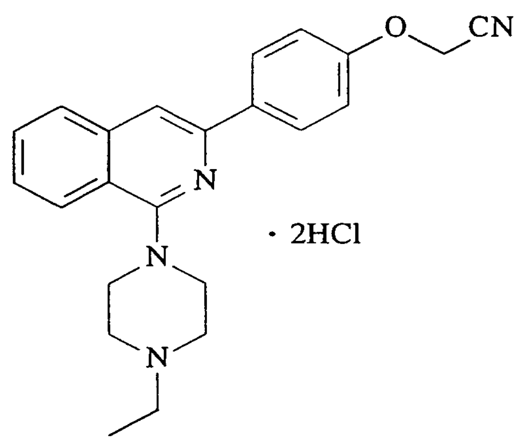
Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.00(s,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,4H), 3.49(q,J=6.0Hz,2H),

3.60(br,4H), 3.73-3.76(m,1H), 4.12(t,J=6.0Hz,2H), 6.90(d,J=8.8Hz,2H), 7.43(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.62(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.12(d,J=8.8Hz,2H).

MS(FAB) m/z 433$(M+H)^+$.

Example 51 Synthesis of 3-(4-cyanomethoxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.30 g) obtained in Example 7 in tetrahydrofuran (15 ml) was added 60% sodium hydride (36 mg) at room temperature. After the evolution of hydrogen was ceased, bromoacetonitrile (0.11 g) was added thereto, and the resulting mixture was reacted at room temperature for 12 hr. Ethyl acetate and an aqueous solution of ammonium chloride were added to the reaction solution. The resulting organic layer was then separated, washed with water, dried and concentrated. To the resulting residue, ethanol and a 2N aqueous solution of hydrochloric acid were added, reacted at 50°C for 30 min, followed by evaporation. The resulting residue was

partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a pale yellow oil. The free compound was converted into a hydrochloride in a conventional manner, to give 0.17 g of the title compound as a yellow powder.

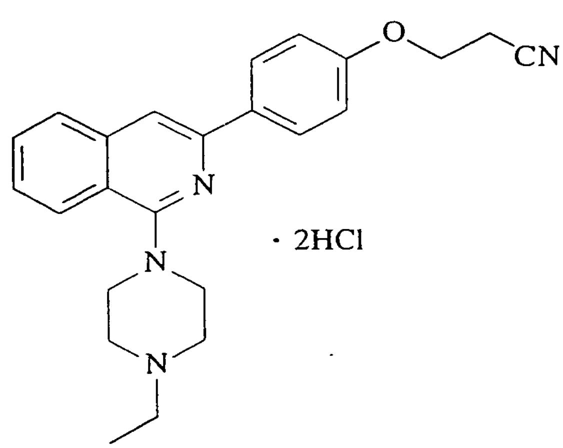
Hydrochloride:

m.p.; 123-125°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.41(m,4H), 3.48-3.65(m,4H), 4.00(br-d,2H), 5.27(s,2H), 7.22(d,J=8.8Hz,2H), 7.60(br-t,1H), 7.74(br-t,1H), 7.97(d,J=8.0Hz,1H), 8.06(s,1H), 8.11(d,J=8.0Hz,1H), 8.22(d,J=8.8Hz,2H), 11.11(m,1H).

MS(ESI) m/z 373(M+H)$^+$.

<u>Example 52 Synthesis of 3-[4-(2-cyanoethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>




To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-

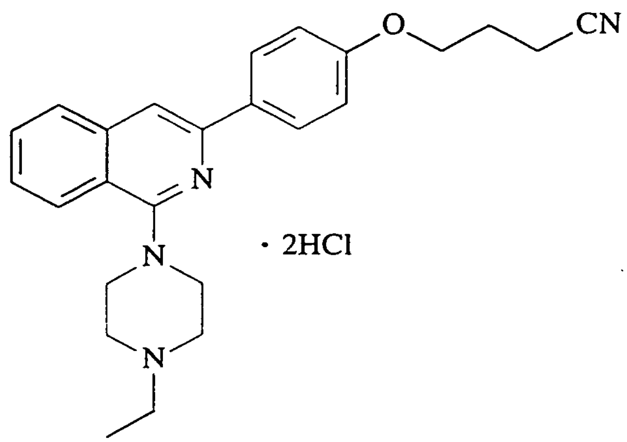
hydroxyphenyl)isoquinoline (0.30 g) obtaiend in Example 7 in acrylonitrile (10 ml) was added hydroxylated N-benzyltrimethylammonium (0.5 g), and the resulting mixture was reacted. The reaction solution was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was remove, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the free compound of the title compound as a pale yellow oil. The free compound was converted into a hydrochloride in a conventional manner, to give the title compound as a yellow powder (0.24 g).

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.37(t,J=7.2Hz,3H), 2.98(t,J=5.2Hz,2H), 3.25-3.55(m,6H), 3.70(br-d,2H), 4.04(br-d,2H), 4.17(t,J=5.2Hz,2H), 6.85(d,J=8.0Hz,2H), 7.36(s,1H), 7.55(d,J=8.0Hz,2H), 7.63(br-t,1H), 7.68(br-d,1H), 7.75(br-t,1H), 7.97(d,J=8.0Hz,2H).

MS(ESI) m/z 387(M+H)$^+$.

Example 53 Synthesis of 3-[4-(3-cyanopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



To a solution of 1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyphenyl)isoquinoline (0.30 g) obtained in Example 7 in tetrahydrofuran (15 ml) was added 60% sodium hydride (36 mg) at room temperature. After the evolution of hydrogen was ceased, bromopropionitrile (0.14 g) was added thereto, and the resulting mixture was reacted at room temperature for 12 hr. Ethyl acetate and an aqueous solution of ammonium chloride were added to the reaction solution, and the resulting organic layer was then separated, washed with water, dried and concentrated. To the resulting residue were added ethanol and a 2N aqueous solution of hydrochloric acid, and the resulting mixture was reacted at 50°C for 30 min, followed by the evaporation. The resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried. The solvent was removed, and the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil. The oil was converted into a hydrochloride in a conventional manner, to give 0.12 g of the title compound

as a yellow powder.

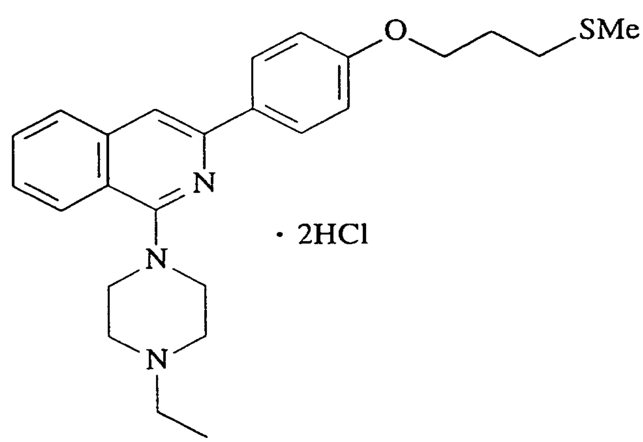
Hydrochloride:

m.p.; 144-146°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.02-2.11(m,2H), 2.70(t,J=7.2Hz,2H), 3.18-3.27(m,2H), 3.34(q,J=7.2Hz,2H), 3.50-3.65(m,4H), 3.98(br-d,2H), 4.12(t,J=6.0Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(br-t,1H), 7.73(br-t,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 11.22(m,1H).

MS(ESI) m/z 401(M+H)$^+$.

Example 54 Synthesis of 3-[4-(3-methylthiopropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




THF (6 ml), DMF (6 ml) and sodium thiomethoxide (270 mg) were added to 3-[4-(3-methanesulfonate propoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline, and then reacted at 80 °C for 10 hr. The reaction solution was partitioned between ethyl acetate and water, and the organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (258 mg, yield;

81%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

Hydrochloride (amorphous):

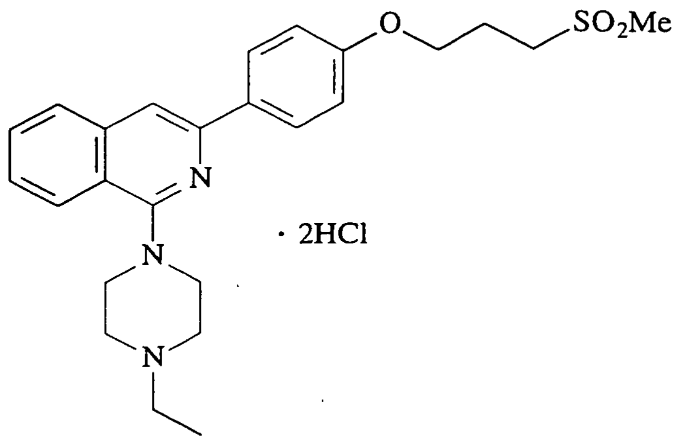
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.88-2.05(m,2H), 2.09(s,3H), 2.65(t,J=7.2Hz,2H), 3.20-3.28(m,2H), 3.30-3.40(m,2H), 3.46-3.53(m,2H), 3.63(d,J=11.2Hz,2H), 3.99(d,J=13.6Hz,2H), 4.13(t,J=6.4Hz,2H), 7.07(d,J=8.8Hz,2H), 7.57(t,J=8.4,Hz,1H), 7.72(t,J=8.4Hz,1H), 7.96(d,J=8.4Hz,1H), 8.00(s,1H), 8.09(d,J=8.4Hz,1H), 8.14(d,J=8.8Hz,2H).

MS(FAB) m/z 422(M+H)$^+$

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.08-2.13(m,2H), 2.14(s,3H), 2.55(q,J=7.2Hz,2H), 2.72(t,J=7.2Hz,2H), 2.77(br,4H), 3.58(br,4H), 4.13(t,J=6.0Hz,2H), 6.99(d,J=8.8Hz,2H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(s,1H), 7.76(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=8.8Hz,2H).

<u>Example 55 Synthesis of 3-[4-(3-Methylsulfonpropoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners as in Examples 161-2 and then 20, the free compound of the title compound was obtained (47 mg, yield; 31%) from 1-bromo-4-(3-methylsulfonpropoxy)benzene (855 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (107 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 113-115°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 2.15-2.22(m,2H), 3.04(s,3H), 3.20-3.28(m,2H), 3.29-3.38(m,4H), 3.49(t,J=12.4Hz,2H), 3.63(d,J=12.0Hz,2H), 3.99(d,J=13.6Hz,2H), 4.17(t,J=6.4Hz,2H), 7.08(d,J=8.8Hz,2H), 7.58(t,J=8.0,Hz,1H), 7.73(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H).

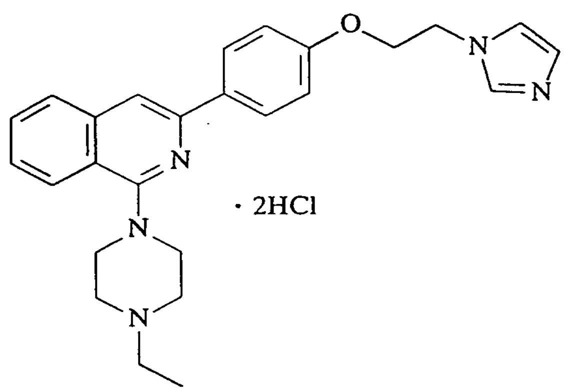
MS(FAB) m/z 454(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.11(t,J=7.2Hz,3H), 2.25-2.35(m,2H), 2.50(q,J=7.2Hz,2H), 2.70(br,4H), 2.89(s,3H),

3.19-3.23(m,2H), 3.52(br,4H), 4.10(t,J=6.0Hz,2H), 6.90(d,J=8.8Hz,2H), 7.36(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.54(s,1H), 7.69(d,J=8.0Hz,1H), 7.98(d,J=8.4Hz,1H), 8.04(d,J=8.8Hz,2H).

Example 56 Synthesis of 3-{4-[2-(1-imidazonyl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



3-[4-(2-Methanesulfonate ethoxy)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (768 mg) was dissolved in DMF (10 ml), to which were then added 60% sodium hydride (221 mg) and imidazole (575 mg), and the resulting mixture was reacted at 60°C overnight. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. Then, the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (576 mg, yield; 80%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.53-3.62(m,2H), 3.94(d,J=13.2Hz,2H), 4.48(d,J=5.2Hz,2H), 4.67(d,J=5.2Hz,1H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.72(s,1H), 7.73(t,J=8.0Hz,1H), 7.89(s,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 9.30(s,1H).

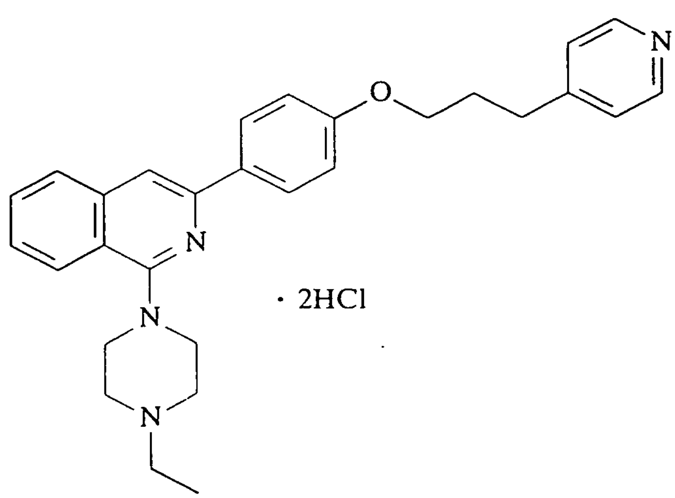
MS(FAB) m/z 428(M+H)$^+$.

m.p.; 160-162°C

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.77(br,4H), 3.58(br,4H), 4.27-4.30(m,2H), 4.36-4.38(m,2H), 4.28-4.30(m,2H), 6.96(d,J=8.8Hz,2H), 7.07-7.09(m,2H), 7.44(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.61(s,1H), 7.62(br,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H).

Example 57 Synthesis of 3-{4-[3-(4-pyridyl)propoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



The free compound of the title compound was obtained (333 mg, yield; 76%) from 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (322 mg) and 2-(3-methanesulfonate propyl)pyridine (417 mg), in the same manner as in Example 51. The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 129-131°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.16-2.24(m,2H), 3.10(t,J=7.2Hz,2H), 3.20-3.26(m,2H), 3.30-3.39(m,2H), 3.46-3.56(m,2H), 3.62(d,J=11.2Hz,2H), 3.97(d,J=13.2Hz,2H), 4.11(t,J=6.0Hz,2H), 7.04(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.00(s,1H), 8.02(d,J=6.8Hz,2H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 8.85(d,J=6.8Hz,2H).

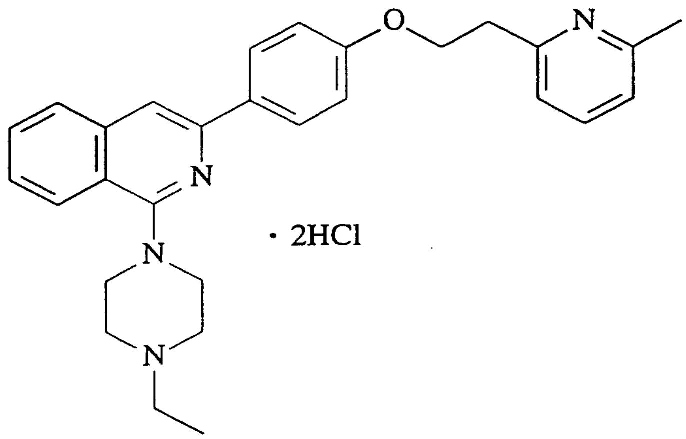
MS(FAB) m/z 453(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.11-2.18(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 2.85(t,J=7.6Hz,2H), 3.58(br,4H), 4.03(t,J=6.0Hz,2H), 6.98(d,J=8.4Hz,2H), 7.16(d,J=4.8Hz,2H), 7.43(t,J=8.0Hz,1H), 7.57(t,J=8.0Hz,1H), 7.62(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.11(d,J=8.4Hz,2H), 8.51(d,J=4.8Hz,1H).

Example 58 Synthesis of 3-{4-[2-(2-methylpyridin-5-yl)ethoxy]phenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline

hydrochloride



DMF (10 ml), potassium carbonate (897 mg) and 2-methyl-5-(2-methanesulfonate ethyl)pyridine (558 mg) were added to 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (432 mg), and the resulting mixture was reacted at 100°C for 3 hr. The reaction solution was thereafter partitioned between ethyl acetate and water, and the resulting organic layer was washed with brine, dried and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (268 mg, yield; 46%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 136-138°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.81(s,3H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.53-3.62(m,4H), 3.95(t,J=13.2Hz,4H), 4.52(t,J=6.4Hz,2H), 7.09(d,J=8.8Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.81(d,J=8.0Hz,1H),

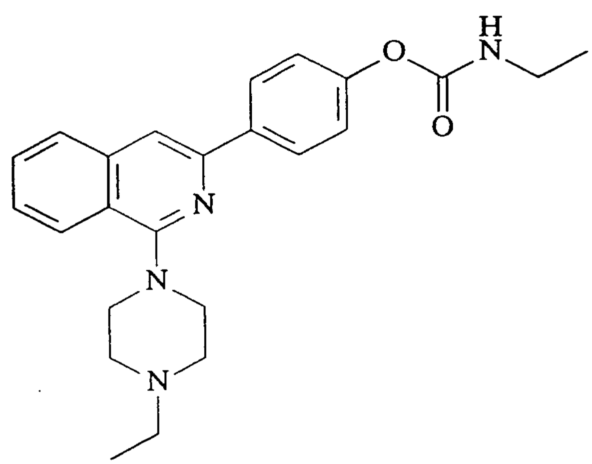
7.90(d,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.01(s,1H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 8.44(t,J=8.0Hz,1H).

MS(FAB) m/z 453$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(s,3H), 2.56(q,J=7.2Hz,2H), 2.75(br,4H), 3.26(t,J=6.8Hz,2H), 3.58(br,4H), 4.41(t,J=6.8Hz,2H), 6.99(d,J=8.8Hz,2H), 7.00-7.03(m,1H), 7.10(d,J=8.0Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(d,J=8.0Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.09(d,J=8.8Hz,2H).

Example 59 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[4-(N-ethylcarbamyl)phenyl]isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-(4-hydroxyphenyl)isoquinoline (333 mg) was dissolved in tetrahydrofuran (5 ml), ethyl isocyanate (800 ml) was added thereto, and then the mixture was stirred at room temperature for 3 hr. The reaction mixture was evaporated. The resulting residue was purified by silica gel column chromatography

(methylene chloride/methanol system), and then recrystallized from ethyl acetate/hexane, to give the free compound of the title compound. The free compound was converted into a hydrochloride in a conventional manner, which was then recrystallized (from ethanol/isopropyl ether), to give the hydrochloride of the title compound as yellow crystals (313 mg, yield; 70%).

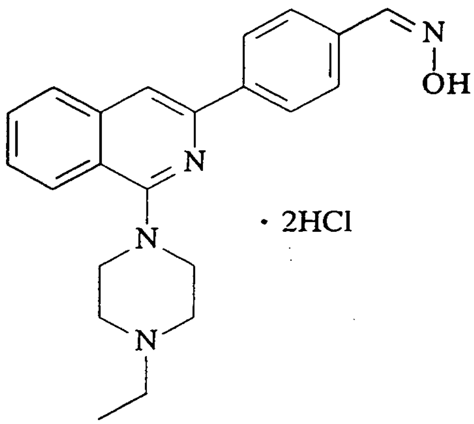
Hydrochloride:

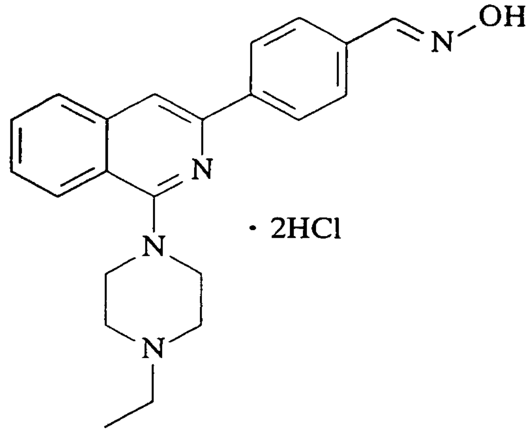
m.p.; 146-150°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.08(3H,t,J=7.2Hz), 1.30(3H,t,J=7.2Hz), 3.05-3.14(2H,m), 3.16-3.24(2H,m), 3.31(1H,t,J=11.6Hz), 3.34(1H,t,J=11.6Hz), 3.49(2H,t,J=13.2Hz), 3.59(2H,d,J=11.6Hz), 3.98(2H,d,J=13.2Hz), 7.21(2H,d,J=8.8Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.72(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.79(1H,t,J=5.6Hz), 7.96(1H,d,J=8Hz), 8.05(1H,s), 8.09(1H,d,J=8Hz), 8.17(2H,d,J=8.8Hz), 10.82(1H,br-s).

ESI-Mass; 405($MH^+$).

Examples 60 and 61 Synthesis of (Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline and (E)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline





1-(4-Ethylpiperazin-1-yl)-3-(4-formylphenyl)isoquinoline (3.00 g) obtained in Example 17-5 was reacted with hydroxylamine hydrochloride (0.90 g) and sodium acetate (1.10 g) in ethanol (50 ml) at 60°C for 2 hr. The reaction solution was evaporated, and then the resulting residue was extracted in methylene chloride, washed with brine and dried. The solvent was removed, and the resulting residue was isolated and purified by silica gel column chromatography (methylene chloride/methanol system), to give (Z)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.01 g) and (E)-1-(4-ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.52 g), both as yellow solids. 0.30 g each of the compounds was converted into a hydrochloride in a conventional manner, to give the hydrochlorides of the title compounds as yellow powders (0.32 g and 0.35g, respectively).

(Example 60)

<u>(Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-</u>

hydroxyiminomethylphenyl)isoquinoline hydrochloride

m.p.; 239°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.50-3.66(m,4H), 3.98-4.06(m,2H), 7.60-7.66(m,1H), 7.74(d,J=8.4Hz,2H), 7.73-7.79(m,1H), 8.00(d,J=8.4Hz,1H), 8.13(d,J=8.8Hz,1H), 8.15(s,1H), 8.21(s,1H), 8.25(d,J=8.4Hz,2H), 11.13(m,1H).

MS(FAB) m/z 361 $(M+H)^+$.

(Example 61)

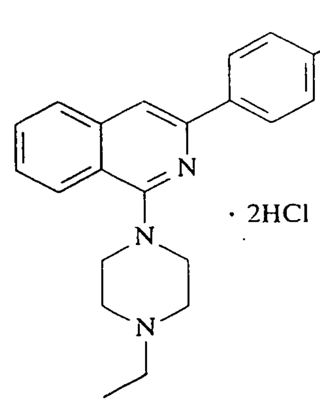
(E)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline hydrochloride

m.p.; 243°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.19-3.29(m,2H), 3.29-3.41(m,2H), 3.48-3.67(m,4H), 3.97-4.06(m,2H), 7.60-7.66(m,1H), 7.73(d,J=8.4Hz,2H), 7.72-7.79(m,1H), 8.00(d,J=8.4Hz,1H), 8.13(d,J=8.8Hz,1H), 8.15(s,1H), 8.21(s,1H), 8.25(d,J=8.4Hz,2H), 10.98(m,1H).

MS(FAB) m/z 361$(M+H)^+$.

Example 62 Synthesis of 3-(4-cyanophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



(E,Z)-1-(4-Ethylpiperazin-1-yl)-3-(4-hydroxyiminomethylphenyl)isoquinoline (1.92 g) obtained in Example 61 was reacted with acetic anhydride in acetic acid at 120°C for 1.5 hr. The reaction solution was evaporated, and to the resulting residue were then added ethyl acetate and a 10% aqueous solution of potassium carbonate, and the mixture was then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 1.78 g of the free compound of the title compound. 0.28 g of the resulting free compound was converted into a hydrochloride in a conventional manner, to give 0.23 g of the title compound as a yellow powder.

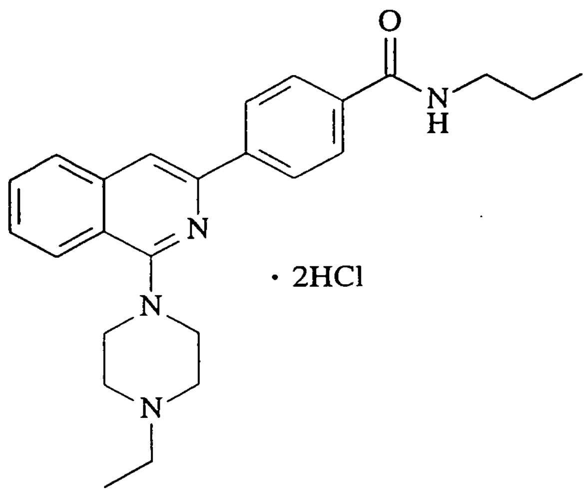
Hydrochloride:

m.p.; 241°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.18-3.28(m,2H), 3.29-3.41(m,2H), 3.51-3.66(m,4H), 3.99-4.07(m,2H), 7.65-7.71(m,1H), 7.77-7.83(m,1H), 7.99(d,J=8.8Hz,2H), 8.03(d,J=8.4Hz,1H), 8.29(s,1H), 8.41(d,J=8.8Hz,2H), 11.20(m,1H).

MS(FAB) m/z 343(M+H)$^+$.

Example 63 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(4-N-propylaminocarbonylphenyl)isoquinoline hydrochloride



(4-N-Propylaminocarbonylphenyl)tributylstannum (1.350 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.820 g) were reacted in the presence of tetrakistriphenylphosphine (0.116 g) in xylene (20 ml) in nitrogen atmosphere overnight. After cooling, the reaction solution was filtered. The resulting filtrate was extracted with a 5N aqueous solution of hydrochloric acid. The resulting aqueous layer was basified with a 5N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and concentrated. The resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 0.578 g of the free compound of the title compound as a pale yellow solid.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.02(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.63-1.73(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br-t,2H), 3.46(dt,J=6.0,7.2Hz,2H), 3.60(br-t,4H), 6.19(br-t,1H), 7.49(br-t,1H), 7.61(br-t,1H), 7.75(s,1H),

7.81(d,J=8.0Hz,1H), 7.86(d,J=8.8Hz,2H), 8.09(d,J=7.6Hz,1H), 8.24(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/ether, to give the title compound as a pale yellow powder.

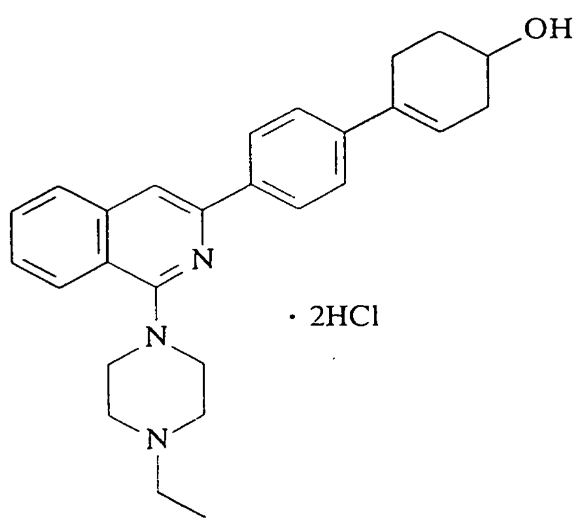
Hydrochloride:

m.p.; 149-150°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.92(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.57(dq,J=7.2Hz,2H), 3.21-3.28(m,2H), 3.32-3.40(m,2H), 3.53(br-t,2H), 3.64(br-d,2H), 4.03(br-d,2H), 7.65(br-t,1H), 7.77(br-t,1H), 7.99(d,J=8.4Hz,2H), 8.02(d,J=7.6Hz,1H), 8.14(d,J=8.4Hz,2H), 8.21(s,1H), 8.28(d,J=8.4Hz,2H), 8.56(t,J=7.2Hz,1H), 10.87(br-s,1H).

MS(FAB) m/z 403(M+H)$^+$.

<u>Example 64 Synthesis of 3-[4-(4-hydroxy-1-cyclohexen-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners as in Examples 161-2 and then 20, an oil was obtained from 1-bromo-4-(4-acetoxy-1-cyclohexen-1-yl)benzene (477 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (200 mg). Methanol (10 ml) and a 1N aqueous solution of sodium hydroxide (1 ml) were added to the resulting oil, and then the mixture was heated under reflux for 1 hr. The reaction solution was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a colorless oil (175 mg, yield; 68%). The oil was converted into a hydrochloride in a conventional manner, to give hydrochloride of the title compound as white crystals.

Hydrochloride:

Melting point; 164-166°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.63(br,1H), 2.44(br,2H), 3.24(t,J=6.0Hz,2H), 3.35-3.40(m,2H), 3.45-3.50(m,2H), 3.63(d,J=11.6Hz,2H), 3.82(br,4H), 4.00(d,J=14.8Hz,2H), 6.17(s,1H), 7.55(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.10(s,1H), 8.11(d,J=8.0Hz,1H), 8.16(d,J=8.4Hz,2H).

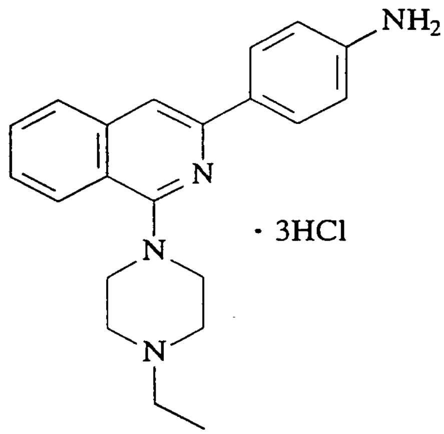
MS(FAB) m/z 414(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.6Hz,3H), 1.86-1.89(m,1H), 2.05-2.10(m,1H), 2.24-2.31(m,1H), 2.55-2.66(m,3H), 2.57(q,J=7.6Hz,2H), 2.77(br,4H), 3.60(br,4H), 4.06-4.14(m,1H),

6.17(s,1H)、7.46(t,J=8.4Hz,1H)、7.50(d,J=8.4Hz,2H)、7.59(t,J=8.4Hz,1H)、7.76(s,1H)、7.79(d,J=8.4Hz,1H)、8.08(d,J=8.4Hz,1H)、8.14(d,J=8.4Hz,2H).

Example 65 Synthesis of 3-(4-aminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



Ethanol (30 ml) and a 2N aqueous solution of hydrochloric acid (4 ml) were added to 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline, and the resulting mixture was stirred at 80°C for 4 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil (71 mg, yield; 7%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 267-268°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.35(t,J=7.2Hz,3H), 3.20-

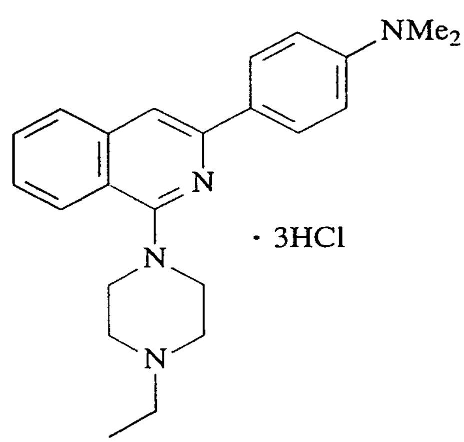
3.26(m,2H), 3.30-3.40(m,2H), 3.56-3.62(m,4H), 4.02(d,J=13.2Hz,2H), 7.54(d,J=8.4Hz,2H), 7.64(t,J=8.0,Hz,1H), 7.77(t,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H), 8.13(s,1H), 8.14(d,J=8.0Hz,1H), 8.31(d,J=8.4Hz,2H).

MS(FAB) m/z 333$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br,4H), 3.57(br,4H), 3.79(br,2H), 6.78(d,J=8.4Hz,2H), 7.49(t,J=8.0Hz,1H), 7.55(t,J=8.0Hz,1H), 7.57(s,1H), 7.74(d,J=8.0Hz,1H), 8.01(d,J=8.4Hz,2H), 8.04(d,J=8.0Hz,1H).

<u>Example 66</u> <u>Synthesis of 3-[4-(N,N-dimethylamino)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride</u>




According to the method of Example 10-1, 3-[4-(N,N-dimethylamino)phenyl]isoquinolin-1-one was obtained from N-methyl-o-toluamide (4.47 g) and 4-(N,N-dimethylamino)benzonitrile.

Subsequently, the resulting 3-[4-(N,N-dimethylamino)]isoquinolin-1-one (2.834 g) was added to

phosphorus oxychloride (25 ml), and the resulting mixture was heated at 110°C for 1.5 hr. The reaction solution was evaporated, and to the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting 1-chloro-3-[4-(N,N-dimethylamino)]isoquinoline was reacted with N-ethylpiperazine (35 ml) at 120°C for 5 hr. The reaction solution was evaporated, and the resulting residue were added ethyl acetate and water. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (chloroform/methanol system), to give 2.687 g of the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.4Hz,3H), 2.55(q,J=7.4Hz,2H), 2.75(br-t,4H), 3.02(s,6H), 3.58(br-t,4H), 6.82(d,J=8.8Hz,2H), 7.38(br-t,1H), 7.53(br-t,1H), 7.58(s,1H), 7.74(d,J=8.4Hz,1H), 8.04(d,J=8.4Hz,1H), 8.09(d,J=8.8Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give the title compound as a yellow powder.

Hydrochloride:

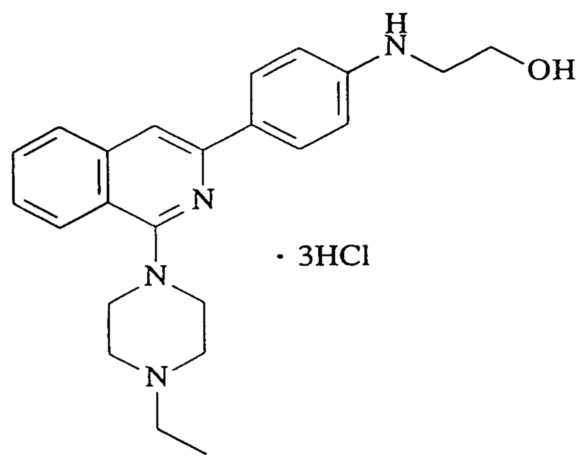
m.p.; 160-162°C (decomp.)

$^1$H-NMR(400MHz, DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.11(s,6H),

3.19-3.25(m,2H), 3.30-3.38(m,2H), 3.55-3.62(m,4H), 4.00(br-d,2H), 7.54(br-s,2H), 7.60(br-t,1H), 7.75(br-t,1H), 7.98(d,J=8.4Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.24(d,J=8.4Hz,2H), 11.31(br-s,1H).

MS(FAB) m/z 361$(M+H)^+$.

Example 67 Synthesis of 3-[4-(2-hydroxyethyl)aminophenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 1-bromo-4-(2-acetoxyethyl)aminobenzene (905 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (266 mg). Ethanol (10 ml) and a 2N aqueous solution of hydrochloric acid (1 ml) were added to the resulting oil, and then the mixture was heated under reflux for 3 hr. The reaction solution was basified with a 1N aqueous solution of sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give an oil

(120 mg, yield; 38%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

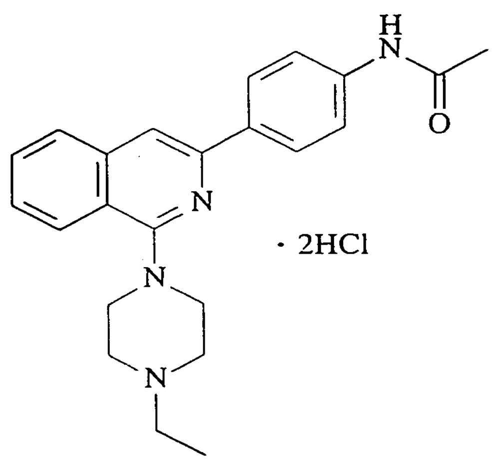
Hydrochloride (amorphous):

MS(FAB) m/z 377(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.39(t,J=5.2Hz,2H), 3.58(br,4H), 3.88(t,J=5.2Hz,2H), 6.75(d,J=8.8Hz,2H), 7.39(t,J=8.4Hz,1H), 7.44(d,J=8.4Hz,1H), 7.54(t,J=8.4Hz,1H), 7.57(s,1H), 7.73(d,J=8.4Hz,1H), 8.04(d,J=8.8Hz,2H).

<u>Example 68</u> <u>Synthesis of 3-(4-acetamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>




In the same manners as in Example 20, the free compound of the title compound was obtained (1.09 g, yield; 40%) from from 1-bromo-4-acetoanilide (5.07 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.3 g). The free compound was converted into a hydrochloride in a conventional manner,

to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

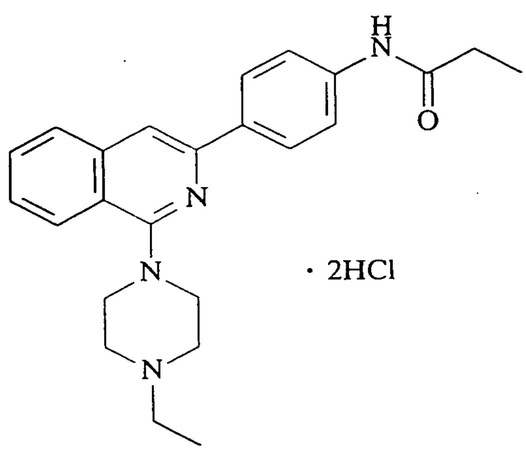
m.p.; 180-182°C

MS(FAB) m/z 375(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 2.21(s,3H), 2.58(q,J=7.2Hz,2H), 2.80(br,4H), 3.62(br,4H), 7.45(t,J=8.0Hz,1H), 7.58(t,J=8.0Hz,1H), 7.61(d,J=8.8Hz,2H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,2H), 8.14(d,J=8.8Hz,2H).

Example 69 Synthesis of 3-(4-ethylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (520 mg, yield; 58%) from 1-bromo-4-ethylcarbonylaminobenzene (3.85 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (745 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 176-178°C

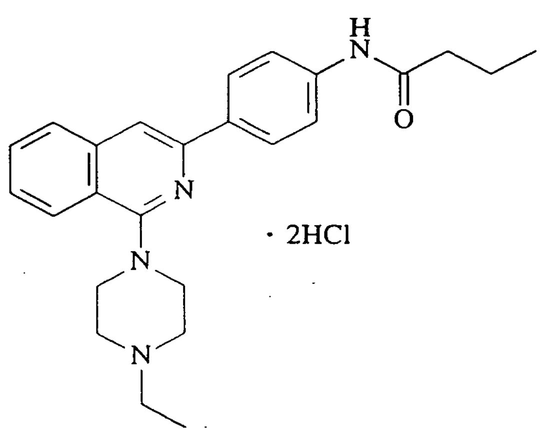
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.11(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 2.38(q,J=7.2Hz,2H), 3.20-3.25(m,2H), 3.32-3.39(m,4H), 3.52(t,J=12.4Hz,2H), 3.62(d,J=11.2Hz,2H), 7.58(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.75(d,J=8.8Hz,2H), 7.96(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.0Hz,1H), 8.15(d,J=8.8Hz,2H), 10.10(s,1H).

MS(FAB) m/z 389(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 1.27(t,J=7.2Hz,3H), 2.42(q,J=7.2Hz,2H), 2.55(q,J=7.2Hz,2H), 2.75(t,J=4.4Hz,4H), 3.58(t,J=4.4Hz,4H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.65(s,1H), 7.76(d,J=8.0Hz,1H), 8.06(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

<u>Example 70</u> <u>Synthesis of 3-(4-propylcarbonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (604 mg, yield; 53%) from 1-bromo-4-propylcarbonylaminobenzene (4.13 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (913 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-172°C

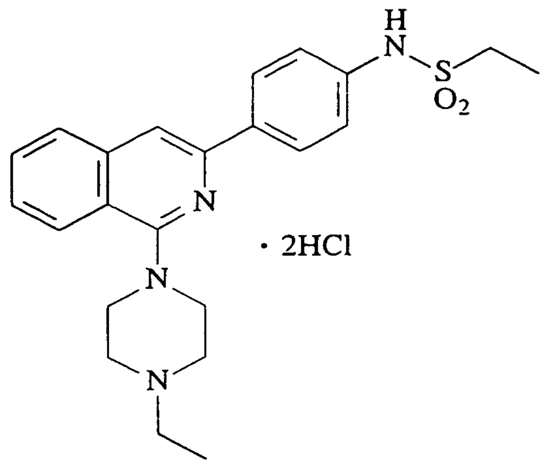
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.94(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.59-1.79(m,2H), 2.35(q,J=7.2Hz,2H), 3.20-3.25(m,2H), 3.30-3.40(m,4H), 3.54-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 7.59(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.78(d,J=8.8Hz,2H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.0Hz,1H), 8.14(d,J=8.8Hz,2H), 10.40(s,1H).

MS(FAB) m/z 403$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.03(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.72-1.82(m,2H), 2.37(t,J=7.2Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.0Hz,4H), 3.58(t,J=4.0Hz,4H), 7.45(dt,J=8.0,1.2Hz,1H), 7.57(dt,J=8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.65(s,1H), 7.77(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 71 Synthesis of 3-(4-ethylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (542 mg, yield; 63%) from 1-bromo-4-ethylsulfonylaminobenzene (3.95 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (648 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 198-201°C

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.22(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 3.15(q,J=7.2Hz,2H), 3.18-3.24(m,2H), 3.30-3.39(m,2H), 3.53-3.62(m,4H), 4.00(d,J=13.6Hz,2H), 7.36(d,J=8.8Hz,2H), 7.59(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.97(d,J=8.0Hz,1H), 8.02(s,1H), 8.10(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H), 10.05(s,1H).

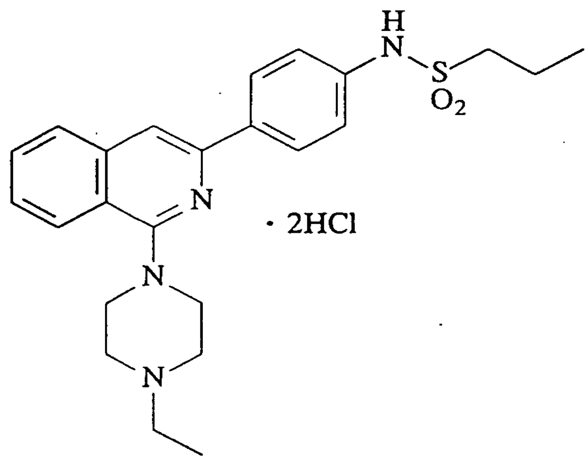
MS(FAB) m/z 425(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.18(t,J=7.2Hz,3H),

1.39(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.18(q,J=7.2Hz,2H), 3.58(br,4H), 7.32(d,J=8.8Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.65(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.8Hz,2H).

Example 72 Synthesis of 3-(4-propylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.31 g, yield; 95%) from 1-bromo-4-propylsulfonylaminobenzene (4.69 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 163-165°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.95(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 1.66-1.76(m,2H), 3.11-3.15(m,2H), 3.20-

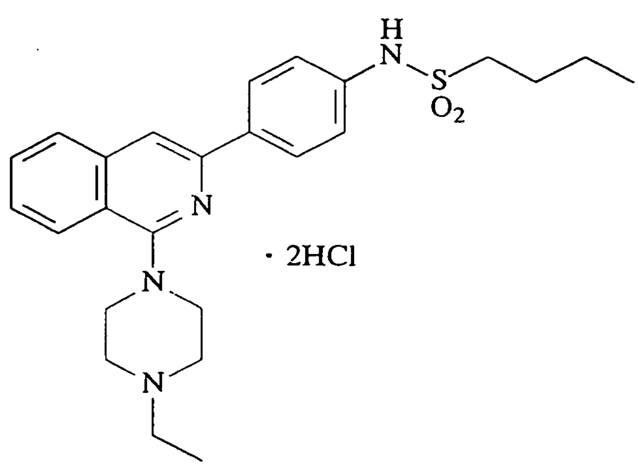
3.25(m,2H), 3.30-3.40(m,2H), 3.51-3.62(m,4H), 4.00(d,J=12.8Hz,2H), 7.35(d,J=8.8Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.02(s,1H), 8.11(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H).

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.91(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.38-1.48(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.11-3.16(m,2H), 3.59(br,4H), 7.31(t,J=8.8Hz,1H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.16(d,J=8.4Hz,2H).

Example 73 Synthesis of 3-(4-butylsulfonylaminophenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (828 mg, yield; 94%) from 1-bromo-4-butylsulfonylaminobenzene (3.51 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline

(620 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 160-163°C

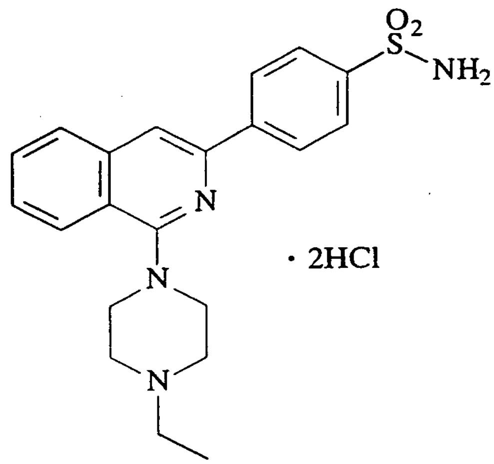
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.84(t,J=7.2Hz,3H), 1.32-1.39(m,5H), 1.64-1.70(m,2H), 3.13-3.17(m,2H), 3.22-3.24(m,2H), 3.33-3.38(m,2H), 3.53-3.62(m,4H), 4.00(d,J=13.2Hz,2H), 7.35(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.97(d,J=8.0Hz,1H), 8.03(s,1H), 8.10(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

MS(FAB) m/z 453(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.03(t,J=7.6Hz,3H), 1.16-1.23(m,5H), 1.83-1.94(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.01-3.13(m,2H), 3.59(br,4H), 7.31(d,J=8.4Hz,2H), 7.47(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.15(d,J=8.4Hz,2H).

Example 74 Synthesis of 3-(4-sulfonamidephenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (49 mg, yield; 7%) from 1-bromo-4-benzenesulfonamide (1.55 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (386 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

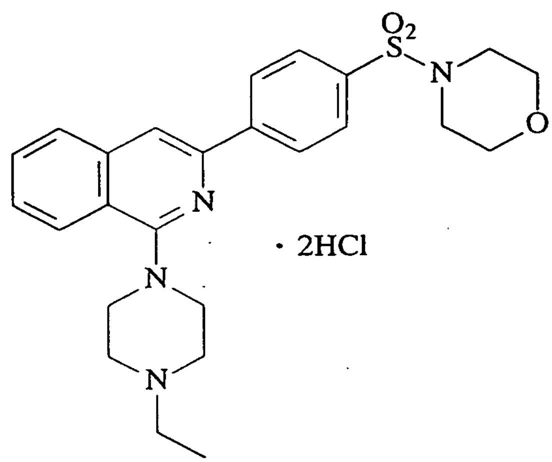
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.21-3.32(m,2H), 3.36-3.42(m,2H), 3.53(t,J=6.8Hz,2H), 3.63(d,J=12.0Hz,2H), 4.05(d,J=13.6Hz,2H), 7.45(s,2H), 7.67(t,J=8.0Hz,1H), 7.79(t,J=8.0,Hz,1H), 7.95(d,J=8.4Hz,2H), 8.02(d,J=8.0Hz,1H), 8.15(d,J=8.0Hz,1H), 8.23(s,1H), 8.38(d,J=8.4Hz,2H).

Free compound:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.08(t,J=7.2Hz,3H), 2.46(q,J=7.2Hz,2H), 2.68(br,4H), 3.47(br,4H), 7.42(s,2H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(ddd,J=8.4,8.0,1.2Hz,1H),

7.94(d,J=8.4Hz,2H), 7.97(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.11(s,1H), 8.37(d,J=8.4Hz,2H).

Example 75 Synthesis of 3-[(4-morpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (620 mg, yield; 49%) from 4-(morpholinylsulfonyl)bromobenzene (2.63 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (872 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

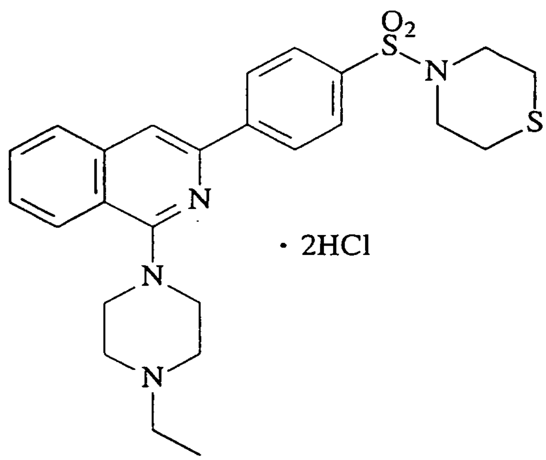
MS(FAB) m/z 467(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(t,J=4.4Hz,4H), 3.06(t,J=4.8Hz,4H), 3.61(t,J=4.4Hz,4H), 3.76(t,J=4.8Hz,4H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(ddd,J=8.4,8.0,1.2Hz,1H),

7.77(s,1H), 7.84(d,J=8.8Hz,2H), 7.85(d,J=8.0Hz,1H), 8.10(d,J=8.4Hz,1H), 8.34(d,J=8.8Hz,2H).

Example 76 Synthesis of 3-[(4-thiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (550 mg, yield; 38%) from 4-(thiomorpholinylsulfonyl)bromobenzene (5.55 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (953 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 268-270°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.69(t,J=4.8Hz,4H), 3.18-3.20(m,6H), 3.32-3.40(m,2H), 3.55-3.64(m,4H), 4.03(d,J=13.6Hz,2H), 7.68(t,J=8.0Hz,1H), 7.80(t,J=8.0,Hz,1H), 7.88(d,J=8.8Hz,2H), 8.05(d,J=8.0Hz,1H),

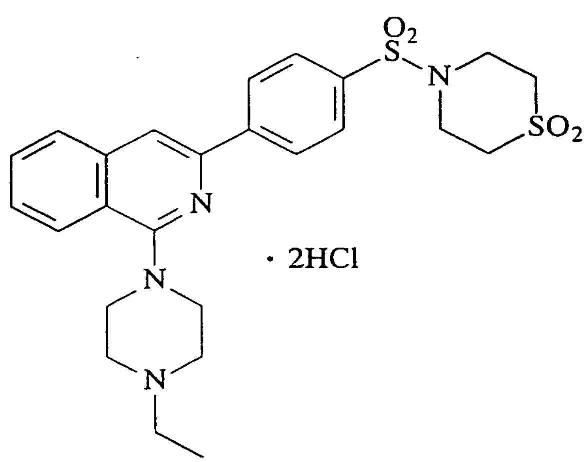
8.16(d,J=8.0Hz,1H), 8.28(s,1H), 8.46(d,J=8.8Hz,2H).

MS(FAB) m/z 483(M+H)$^+$

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.72-2.74(m,2H), 2.79(br,4H), 3.38-3.41(m,2H), 3.62(br,4H), 7.53(dt,J=8.0,1.2Hz,1H), 7.64(dt,J=8.0,1.2Hz,1H), 7.70(s,1H), 7.82(d,J=8.8Hz,2H), 7.83(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.32(d,J=8.8Hz,2H).

Example 77 Synthesis of 3-[(1,1-dioxythiomorpholinyl)sulfonylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (673 mg, yield; 52%) from 1-bromo-4-(1,1-dioxythiomorpholinyl)sulfonylbenzene (3.59 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (811 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as

yellow crystals.

Hydrochloride:

m.p.; 198-200°C

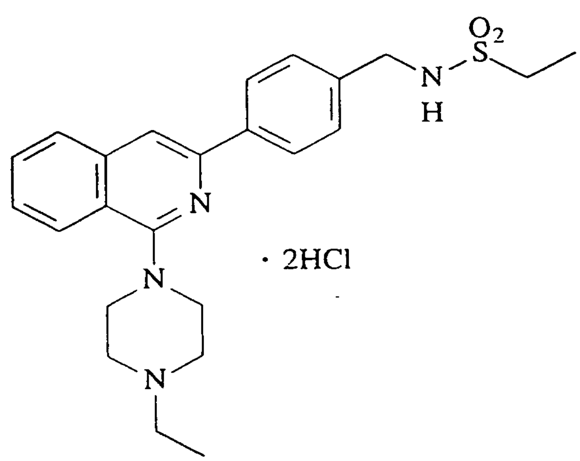
$^1$H-NMR(400MHz,DMSO-$d_6$); δ(ppm) 1.34(t,J=7.2Hz,3H), 3.22-3.25(m,2H), 3.29-3.40(m,6H), 3.51-3.55(m,6H), 3.61(t,J=11.6Hz,2H), 4.04(d,J=13.6Hz,2H), 7.69(dt,J=8.0,1.2Hz,1H), 7.81(dt,J=8.0,1.2Hz,1H), 7.95(d,J=8.4Hz,2H), 8.05(d,J=8.0Hz,1H), 8.16(d,J=8.0Hz,1H), 8.30(s,1H), 8.49(d,J=8.4Hz,2H).

MS(FAB) m/z 515(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,DMSO-$d_6$); δ(ppm) 1.10(br-t,3H), 2.66(br,2H), 3.29-3.31(m,4H), 3.34(br,4H), 3.49(br,8H), 7.64(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.94(d,J=8.8Hz,2H), 8.00(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.19(s,1H), 8.48(d,J=8.8Hz,2H).

Example 78 Synthesis of 3-(4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (655 mg, yield; 49%) from 1-bromo-4-ethylsulfonylaminobenzene (2.73 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (975 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

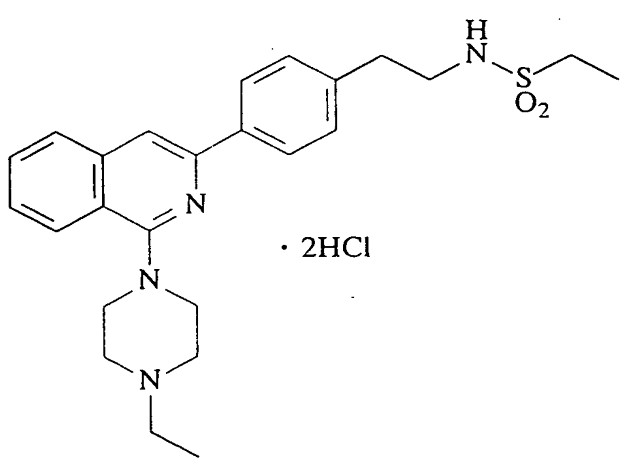
Hydrochloride:

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.6Hz,3H), 1.35(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.00(q,J=7.6Hz,2H), 3.59(br,4H), 4.37(d,J=6.0Hz,2H), 4.59(br,1H), 7.45(d,J=8.4Hz,2H), 7.48(t,J=8.4Hz,1H), 7.60(t,J=8.4Hz,1H), 7.70(s,1H), 7.80(d,J=8.4Hz,1H), 8.09(d,J=8.4Hz,1H), 8.18(d,J=8.4Hz,2H).

Example 79 Synthesis of 3-(4-ethylsulfonylaminoethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.22 g, yield; 76%) from 1-bromo-4-ethylsulfonylaminoethylbenzene (3.54 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.14 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 194-197°C

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.16(t,J=7.2Hz,3H), 1.34(t,J=7.2Hz,3H), 2.84(t,J=7.2Hz,2H), 2.97(q,J=7.2Hz,2H), 3.19-3.24(m,4H), 3.33-3.39(m,2H), 3.56-3.63(m,4H), 4.00(d,J=13.2Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(dt,J=8.0,1.2Hz,1H), 7.75(dt,J=8.0,1.2Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.13(d,J=8.4Hz,2H).

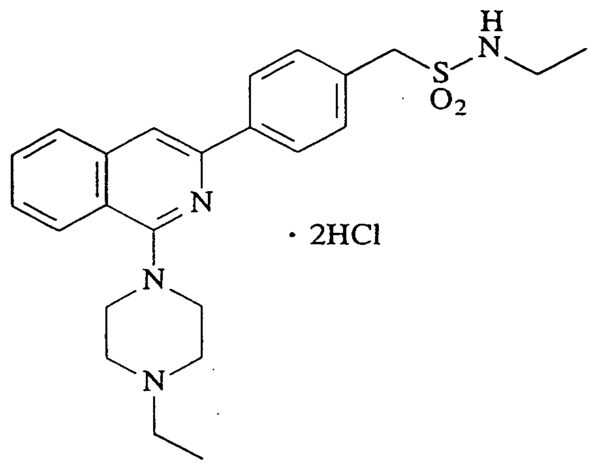
MS(FAB) m/z 453(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.17(t,J=7.2Hz,3H), 1.28(t,J=7.6Hz,3H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.92(t,J=6.4Hz,2H), 2.96(q,J=7.6Hz,2H), 3.41(t,J=6.4Hz,2H), 3.59(br,4H), 4.36(t,J=6.4Hz,1H), 7.30(d,J=8.4Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 80 Synthesis of 3-(4-

ethylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (449 mg, yield; 60%) from 1-bromo-4-ethylaminosulfonylmethylbenzene (1.28 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (550 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 154-156°C

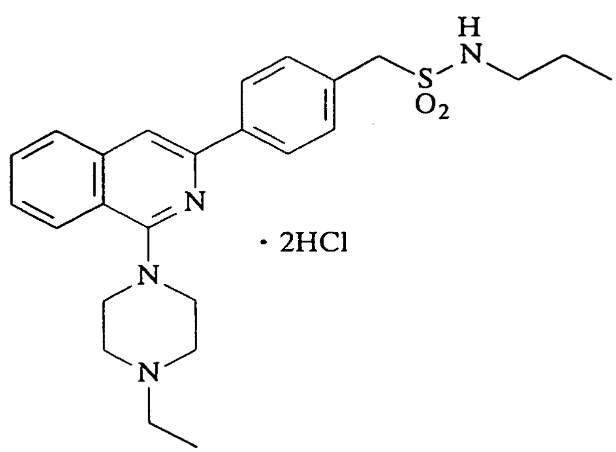
$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.03(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 2.90-3.00(m,2H), 3.18-3.25(m,2H), 3.30-3.40(m,2H), 3.49-3.62(m,4H), 3.99(d,J=13.6Hz,2H), 4.37(s,2H), 7.09(br,1H), 7.48(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.10(s,1H), 8.11(d,J=8.0Hz,1H), 8.18(d,J=8.4Hz,2H).

MS(FAB) m/z 439$(M+H)^+$.

Free compound:

$^1H$-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.14-1.20(m,6H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 3.10(dd,J=7.2,6.0Hz,2H), 3.60(br,4H), 4.07(t,J=6.0Hz,1H), 4.31(s,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(d,J=8.4Hz,2H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.19(d,J=8.4Hz,2H).

Example 81 Synthesis of 3-(4-propylaminosulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (307 mg, yield; 28%) from 1-bromo-4-propylaminosulfonylmethylbenzene (1.62 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (766 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 194-197°C

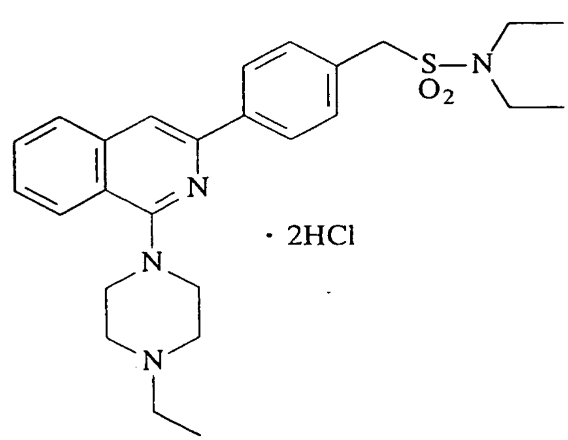
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.83(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 1.38-1.48(m,2H), 2.86-2.90(m,2H), 3.18-3.25(m,2H), 3.31-3.37(m,2H), 3.50-3.61(m,4H), 3.97-4.02(m,2H), 4.37(s,2H), 7.11(br,1H), 7.48(d,J=8.0Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.09(s,1H), 8.10(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,2H).

MS(FAB) m/z 453(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.91(t,J=7.2Hz,3H), 1.19(t,J=7.2Hz,3H), 1.54(q,J=7.2Hz,2H), 2.58(q,J=7.2Hz,2H), 2.79(br,4H), 3.02(q,J=7.2Hz,2H), 3.62(br,4H), 4.08(t,J=6.0Hz,1H), 4.32(s,2H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(d,J=8.4Hz,2H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H), 8.19(d,J=8.4Hz,2H).

Example 82 Synthesis of 3-[4-(N,N-diethylamino)sulfonylmethylphenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (101 mg, yield; 17%) from 1-bromo-4-N,N-diethylaminosulfonylmethylbenzene (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (530 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

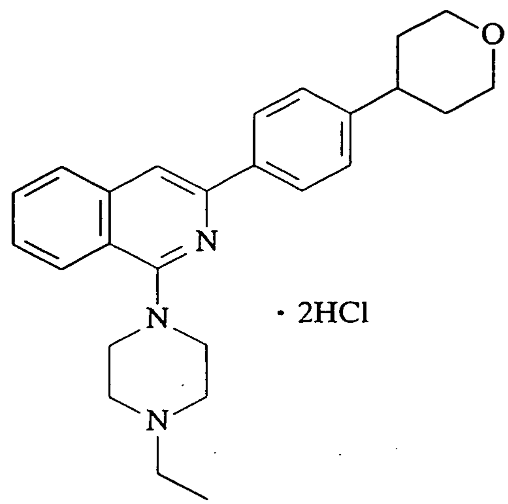
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.04(t,J=7.2Hz,6H), 1.31(t,J=7.2Hz,3H), 3.10(q,J=7.2Hz,4H), 3.18-3.25(m,2H), 3.30-3.38(m,2H), 3.51-3.61(m,4H), 4.00(d,J=13.2Hz,2H), 4.43(s,2H), 7.50(d,J=8.4Hz,2H), 7.60(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.11(s,1H), 8.20(d,J=8.4Hz,2H).

MS(FAB) m/z 467(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.12(t,J=7.2Hz,6H), 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,4H), 3.13(q,J=7.2Hz,4H), 3.61(br,4H), 4.27(s,2H), 7.46-7.50(m,1H), 7.48(d,J=8.0Hz,2H), 7.06(t,J=8.0Hz,1H), 7.72(s,1H), 7.80(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.19(d,J=8.0Hz,2H).

Example 83 Synthesis of 3-[4-(tetrahydropyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



Methanol (80 ml) and platinum oxide (100 mg) were added to 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (2.3 g), and the mixture was reacted at room temperature for 2 hr. The reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified with a 1N aqueous solution of sodium hydroxide, and then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. Then, the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give an oil (905 mg, yield; 47%). The oil was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 148-150°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.70-1.76(m,4H), 2.85(br,1H), 3.20-3.28(m,2H), 3.30-3.38(m,2H),

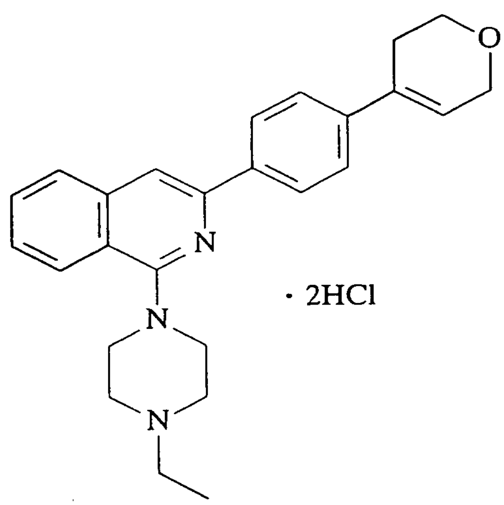
3.44-3.56(m,4H), 3.63(d,J=11.6Hz,2H), 3.95-4.01(m,4H), 7.40(d,J=8.4Hz,2H), 7.60(t,J=8.4Hz,1H), 7.74(t,J=8.4Hz,1H), 7.99(d,J=8.4Hz,1H), 8.06(s,1H), 8.11(d,J=8.4Hz,1H), 8.14(d,J=8.4Hz,2H).

MS(FAB) m/z 402$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.69-1.93(m,4H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 2.75-2.88(m,1H), 3.53-3.59(m,2H), 3.59(br,4H), 4.09-4.13(m,2H), 7.33(d,J=8.4Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(s,1H), 7.78(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 84 Synthesis of 3-[4-(5,6-dihydro-2H-pyran-4-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (443 mg, yield; 58%) from 1-bromo-(5,6-dihydro-2H-pyran-4-

yl)benzene (2.3 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-172°C

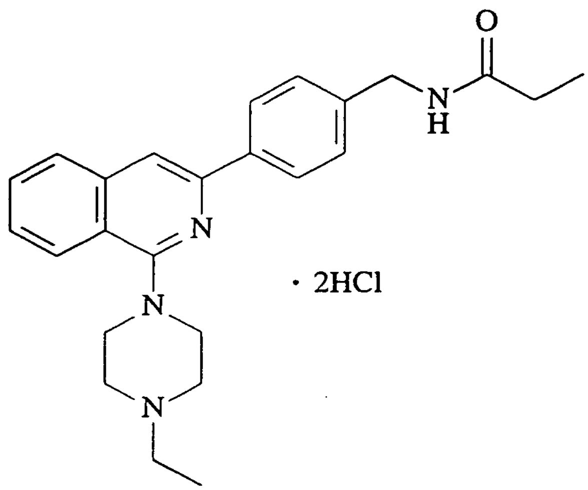
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.38(m,2H), 3.32-3.40(m,2H), 3.54(t,J=13.6Hz,4H), 3.63(d,J=12.0Hz,2H), 3.86(t,J=5.6Hz,2H), 4.01(d,J=14.0Hz,2H), 4.27(br,2H), 6.38(br,1H), 7.60(d,J=8.8Hz,2H), 7.61(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.11(s,1H), 8.13(d,J=8.0Hz,1H), 8.20(d,J=8.8Hz,2H).

MS(FAB) m/z 400$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.52-2.58(m,2H), 2.54(q,J=7.2Hz,2H), 2.75(br,4H), 3.59(br,4H), 3.95(t,J=5.6Hz,2H), 4.35(t,J=2.8Hz,2H), 6.20(br,1H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.48(d,J=8.8Hz,2H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.77(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.14(d,J=8.8Hz,2H).

Example 85 Synthesis of 3-(4-ethylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (608 mg, yield; 59%) from 1-bromo-4-ethylcarbonylaminomethylbenzene (2.31 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (808 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

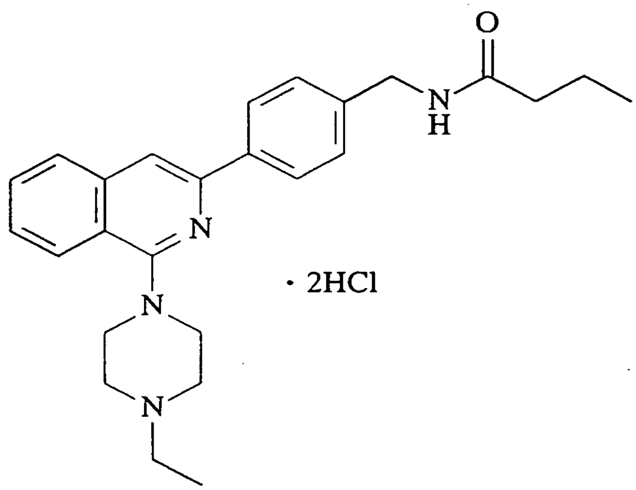
Hydrochloride:

m.p.; 171-174°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.05(t,J=7.6Hz,3H), 1.33(t,J=7.2Hz,3H), 2.17(q,J=7.6Hz,2H), 3.15-3.28(m,2H), 3.30-3.38(m,2H), 3.53(t,J=12.8Hz,2H), 3.61(d,J=11.2Hz,2H), 3.99(d,J=12.8Hz,2H), 4.32(d,J=6.0Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.15(d,J=8.4Hz,2H), 8.37(t,J=6.0Hz,1H).

MS(FAB) m/z 403(M+H)$^+$.

Example 86 Synthesis of 3-(4-propylcarbonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (777 mg, yield; 52%) from 1-bromo-4-propylcarbonylaminomethylbenzene (2.34 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.14 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 126-128°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.88(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.57(q,J=7.2Hz,2H), 2.15(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.52-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 4.33(d,J=6.0Hz,2H), 7.38(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H),

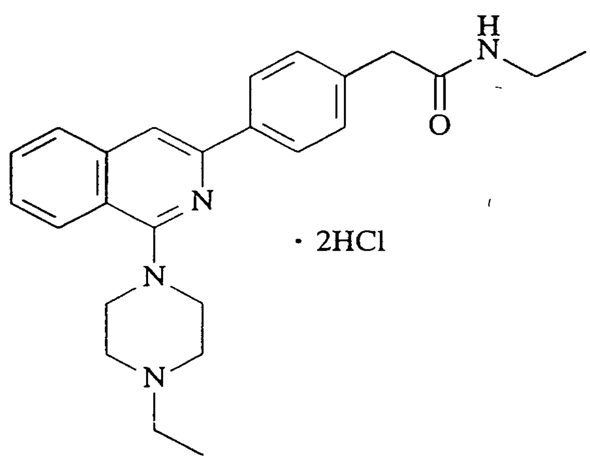
8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H), 8.40(t,J=6.0Hz,1H).

MS(FAB) m/z 417(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.98(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.67-1.76(m,2H), 2.22(t,J=7.2Hz,2H), 2.55(q,J=7.2Hz,2H), 2.76(br,4H), 3.59(br,4H), 4.50(d,J=5.6Hz,2H), 5.75(br,1H), 7.37(d,J=8.4Hz,2H), 7.46(t,J=8.0Hz,1H), 7.59(t,J=8.0Hz,1H), 7.68(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,2H).

Example 87 Synthesis of 3-(4-ethylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (587 mg, yield; 56%) from 1-bromo-4-ethylaminocarbonylmethylbenzene (1.29 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (830 mg). The free compound

was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 143-145°C

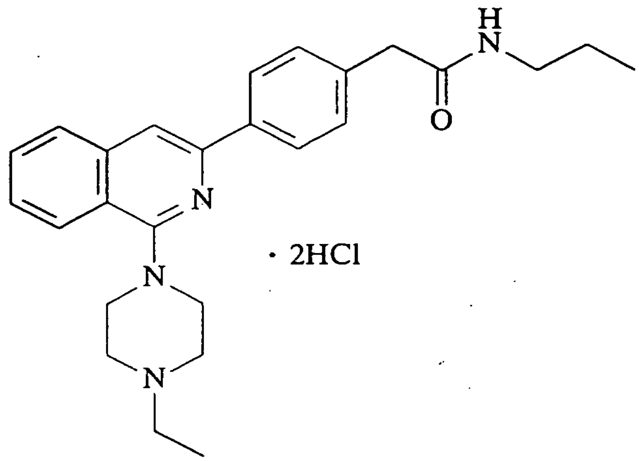
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.03(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 3.06-3.12(m,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.46(s,2H), 3.52-3.63(m,4H), 4.00(d,J=13.2Hz,2H), 7.39(d,J=8.4Hz,2H), 7.60(dt,J=8.0,1.2Hz,1H), 7.74(dt,J=8.0,1.2Hz,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

MS(FAB) m/z 403(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.61(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.78(br,4H), 3.23-3.29(m,2H), 3.60(br,4H), 3.64(s,2H), 5.40(br,1H), 7.35(d,J=8.4Hz,2H), 7.45(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 88 Synthesis of 3-(4-propylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (517 mg, yield; 56%) from 1-bromo-4-propylaminocarbonylmethylbenzene (2.01 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (706 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 138-141°C

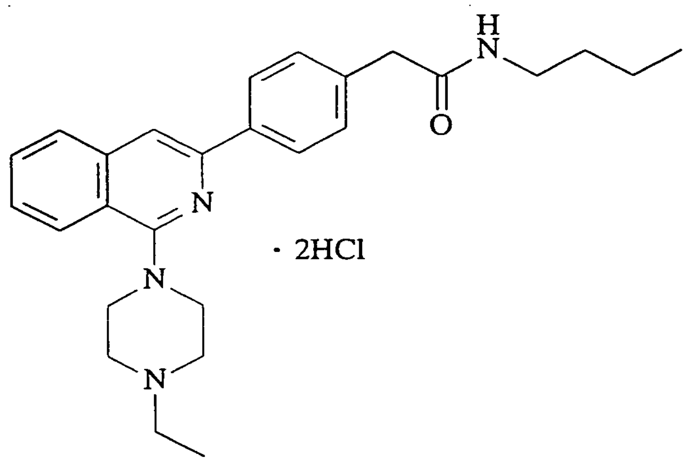
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.84(t,J=7.2Hz,3H), 1.33(t,J=7.2Hz,3H), 1.40-1.45(m,2H), 3.03(q,J=7.2Hz,2H), 3.22(t,J=7.2Hz,2H), 3.30-3.40(m,2H), 3.47(s,2H), 3.52-3.63(m,4H), 4.01(d,J=13.2Hz,2H), 7.39(d,J=8.0Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.07(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,2H).

MS(FAB) m/z 417(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 0.84(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.40-1.50(m,2H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 3.18(q,J=6.4Hz,2H), 3.59(br,4H), 3.65(s,2H), 5.42(br,1H), 7.36(d,J=8.4Hz,2H), 7.48(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.70(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 89 Synthesis of 3-(4-butylaminocarbonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (615 mg, yield; 67%) from 1-bromo-4-butylaminocarbonylmethylbenzene (1.75 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (679 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 133-136°C

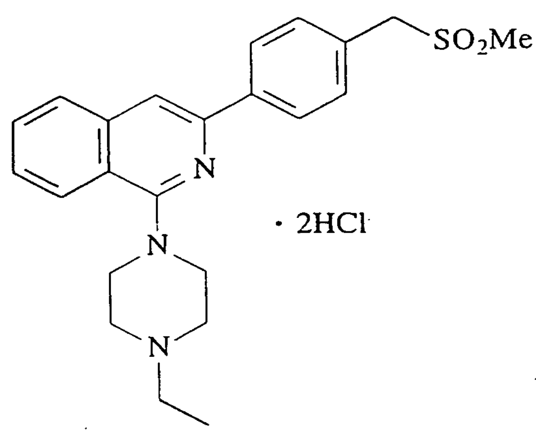
$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 0.87(t,J=7.2Hz,3H), 1.27-1.42(m,7H), 3.06(q,J=6.4Hz,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.47(s,2H), 3.51-3.63(m,4H), 4.00(d,J=13.6Hz,2H), 7.39(d,J=8.4Hz,2H), 7.61(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.06(s,1H), 8.11(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

MS(FAB) m/z 431(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 0.88(t,J=7.2Hz,3H), 1.18(t,J=7.2Hz,3H), 1.32-1.42(m,2H), 1.37-1.44(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.21(q,J=6.4Hz,2H), 3.59(br,4H), 3.64(s,2H), 5.39(br,1H), 7.35(d,J=8.4Hz,2H), 7.48(t,J=8.0Hz,1H), 7.60(t,J=8.0Hz,1H), 7.71(s,1H), 7.80(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.17(d,J=8.4Hz,2H).

Example 90 Synthesis of 3-(4-methylsulfonylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (430

mg, yield; 49%) from 1-bromo-4-methylsulfonylmethylbenzene (1.26 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (685 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 260-262°C

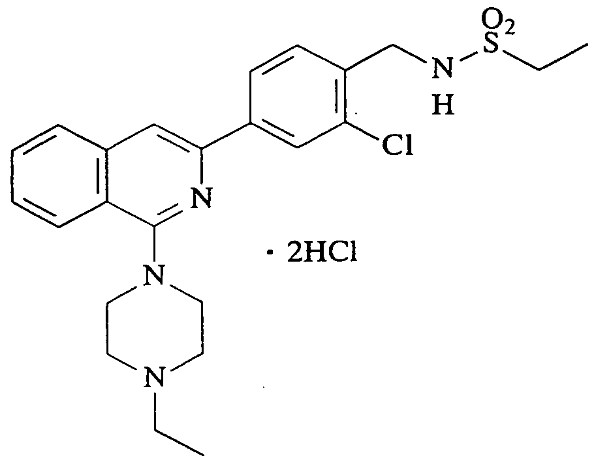
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.95(s,3H), 3.18-3.28(m,2H), 3.30-3.38(m,2H), 3.55-3.63(m,4H), 4.02(d,J=13.6Hz,2H), 4.57(s,2H), 7.55(d,J=8.4Hz,2H), 7.63(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 8.00(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H), 8.13(s,1H), 8.23(d,J=8.4Hz,2H).

MS(FAB) m/z 410(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.79(s,2H), 3.59(br,4H), 4.32(s,2H), 7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.51(d,J=8.4Hz,2H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(s,1H), 7.81(d,J=8.0Hz,1H), 8.09(d,J=8.4Hz,1H), 8.22(d,J=8.0Hz,2H).

Example 91 Synthesis of 3-(3-chloro-4-ethylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (101 mg, yield; 17%) from 3-chloro-4-ethylsulfonylaminomethyl-bromobenzene (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (530 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 278-280°C (decomp.)

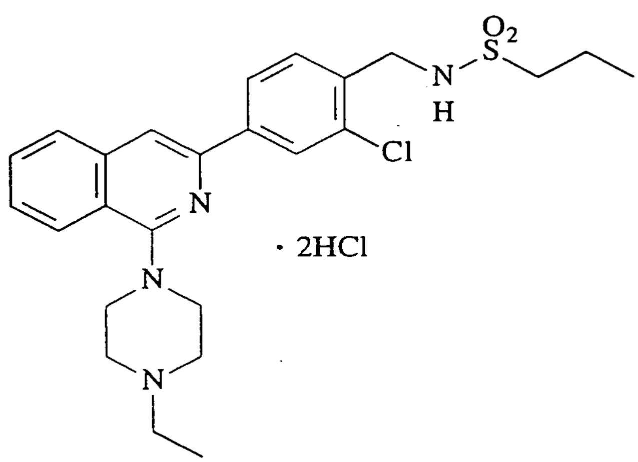
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 1.31(t,J=7.2Hz,3H), 3.04(q,J=7.2Hz,2H), 3.18-3.25(m,2H), 3.28-3.37(m,2H), 3.51(t,J=12.8Hz,2H), 3.62(d,J=11.6Hz,2H), 3.97-4.03(m,2H), 4.29(d,J=6.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.66(d,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H), 8.18(dd,J=8.0,1.6Hz,1H), 8.18(s,1H), 8.24(d,J=1.6Hz,1H).

MS(FAB) m/z 473(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.30(t,J=7.6Hz,3H), 2.56(q,J=7.2Hz,2H), 2.77(br,4H), 2.93(q,J=7.6Hz,2H), 3.59(br,4H), 4.45(d,J=6.4Hz,2H), 4.88(br,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(d,J=8.0Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(s,1H), 7.80(d,J=8.4Hz,1H), 8.05(dd,J=8.0,1.6Hz,1H), 8.08(d,J=8.4Hz,1H), 8.23(d,J=1.6Hz,1H).

Example 92 Synthesis of 3-(3-chloro-4-propylsulfonylaminomethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (365 mg, yield; 39%) from 3-chloro-4-propylsulfonylaminomethyl-bromobenzene (1.58 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (825 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 253-255°C (decomp.)

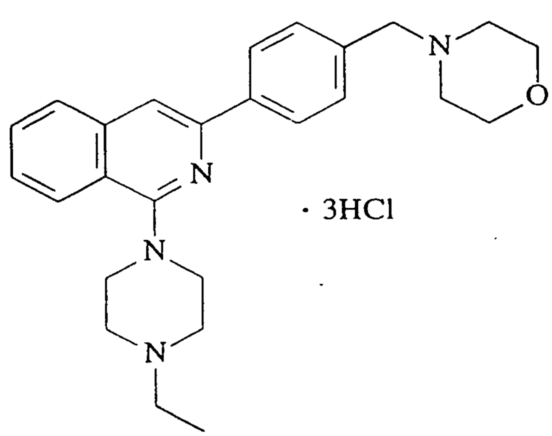
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.94(t,J=7.6Hz,3H), 1.31(t,J=7.2Hz,3H), 1.62-1.74(m,2H), 2.98-3.02(m,2H), 3.18-3.25(m,2H), 3.30-3.38(m,2H), 3.50(t,J=12.8Hz,2H), 3.62(d,J=11.6Hz,2H), 3.99(d,J=13.2Hz,2H), 4.28(d,J=6.0Hz,2H), 7.62(t,J=8.0Hz,1H), 7.65(d,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H), 8.18(dd,J=8.0,2.0Hz,1H), 8.18(s,1H), 8.24(d,J=2.0Hz,1H).

MS(FAB) m/z 488(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.96(t,J=7.6Hz,3H), 1.19(t,J=7.2Hz,3H), 1.76-1.81(m,2H), 2.57(q,J=7.2Hz,2H), 2.77(br,4H), 2.87-2.91(m,2H), 3.59(br,4H), 4.45(d,J=6.4Hz,2H), 4.82(t,J=6.4Hz,1H), 7.50(t,J=8.4Hz,1H), 7.52(d,J=8.0Hz,1H), 7.61(t,J=8.4Hz,1H), 7.68(s,1H), 7.80(d,J=8.4Hz,1H), 8.05(dd,J=8.0,1.6Hz,1H), 8.08(d,J=8.4Hz,1H), 8.23(d,J=1.6Hz,1H).

Example 93 Synthesis of 3-(4-morpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (472 mg, yield; 71%) from 4-morpholinylmethyl-bromobenzene (1.02 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (651 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a yellow amorphous.

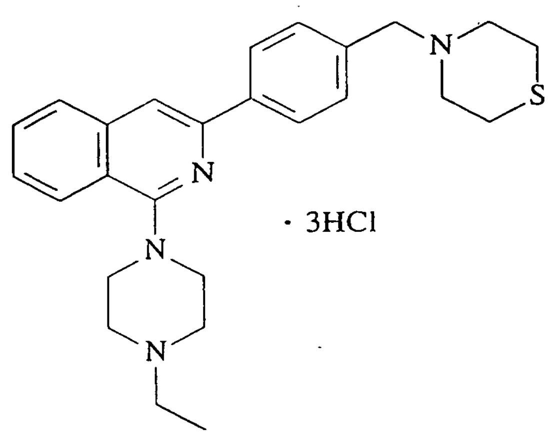
Hydrochloride (amorphous):

MS(FAB) m/z 417(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.49(t,J=4.8Hz,4H), 2.54(q,J=7.2Hz,2H), 2.77(br,4H), 3.56(s,2H), 3.60(br,4H), 3.73(t,J=4.8Hz,4H), 7.42(d,J=8.4Hz,2H), 7.46(dt,J=8.0,1.2Hz,1H), 7.59(dt,J=8.0,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.08(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,2H).

Example 94 Synthesis of 3-(4-thiomorpholinylmethylphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and

20, the free compound of the title compound was obtained (273 mg, 22%) from 4-thiomorpholinylmethyl-bromobenzene (1.08 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (882 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 193-197°C

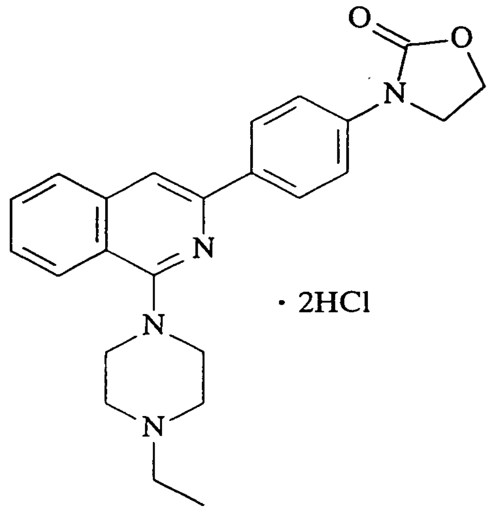
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.81(d,J=14.4Hz,2H), 3.08-3.16(m,2H), 3.21-3.38(m,6H), 3.53-3.65(m,6H), 4.01(d,J=12.8Hz,2H), 4.40(d,J=5.2Hz,2H), 7.64(t,J=8.0Hz,1H), 7.77(t,J=8.0Hz,1H), 7.79(d,J=8.4Hz,2H), 8.01(d,J=8.0Hz,1H), 8.14(d,J=8.0Hz,1H), 8.17(s,1H), 8.28(d,J=8.4Hz,2H).

MS(FAB) m/z 433$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.56(t,J=7.2Hz,4H), 2.68-2.77(m,10H), 3.58(s,2H), 3.68(br,4H), 7.40(d,J=8.0Hz,2H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.69(s,1H), 7.79(d,J=8.0Hz,1H), 8.07(d,J=8.4Hz,1H), 8.12(d,J=8.0Hz,2H).

Example 95 Synthesis of 3-[4-(3-oxazolidinone)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (1.0 g, yield; 71%) was obtained from 1-bromo-4-(3-oxazolidinone)benzene (2.29 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.19 g). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 171-174°C

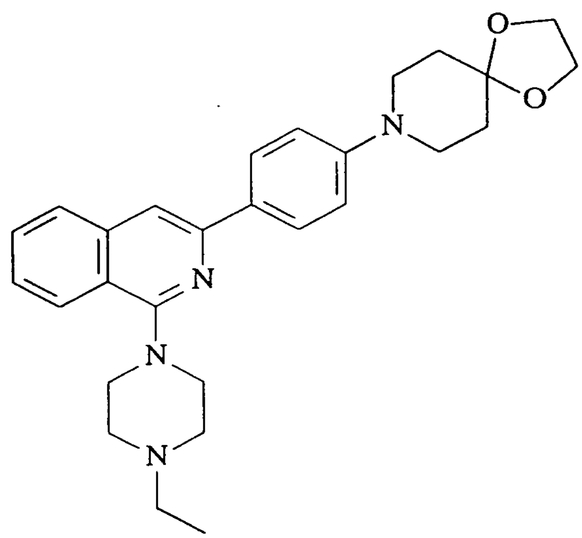
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.32-3.39(m,2H), 3.54(t,J=12.8Hz,2H), 3.62(d,J=10.8Hz,2H), 4.02(d,J=13.6Hz,2H), 4.14(t,J=8.0Hz,2H), 4.46-4.50(m,2H), 7.60(t,J=8.0Hz,1H), 7.71(d,J=8.8,Hz,2H), 7.74(t,J=8.0Hz,1H), 7.98(d,J=8.0Hz,1H), 8.08(s,1H), 8.11(d,J=8.0Hz,1H), 8.24(d,J=8.8Hz,2H).

MS(FAB) m/z 403(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.79(br,4H), 3.61(br,4H), 4.04-4.08(m,2H), 4.44-4.48(m,2H), 7.44(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(d,J=8.8Hz,2H), 7.65(s,1H), 7.76(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.16(d,J=8.8Hz,2H).

Example 96 Synthesis of 3-[4-(4,4-ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.72 g) and 4-(4,4-ethylenedioxypiperidin-1-yl)phenyltributylstannum (3.12 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.5 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated, and ethyl acetate and an aqueous saturated solution of sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate and evaporated. The resulting residue was purified by silica gel column

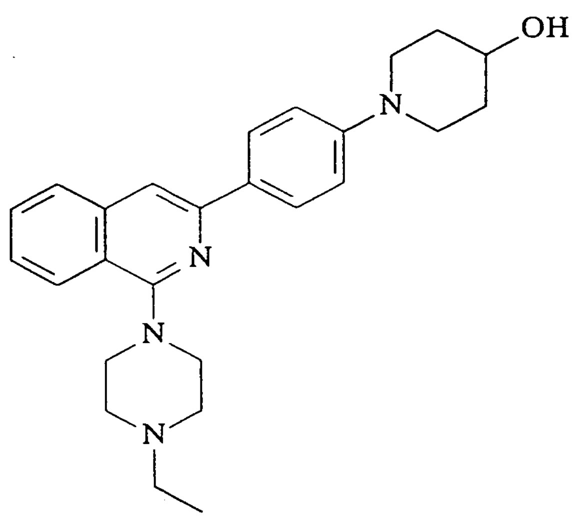
chromatography (methylene chloride/methanol system), to give 1.27 g of the title compound as a white powder.

Free compound:

m.p.; 118°C

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.87(br-t,4H), 2.55(q,J=7.2Hz,2H), 2.75(br-s,4H), 3.42(m,4H), 3.58(br-s,4H), 4.01(s,4H), 7.03(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(dd,J=8.8Hz,2H).

Example 97 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-hydroxypiperidin-1-yl)phenyl]isoquinoline trihydrochloride




3-[4-(4,4-Ethylenedioxypiperidin-1-yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline (290 mg) obtained in Example 96 was treated with camphorsulfonic acid and methanol. Then, a 2N aqueous solution of hydrochloric acid (50 ml) was added thereto, and the mixture was reacted for 1 hr. The reaction solution was basified and extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and

dried over magnesium sulfate. The solvent was evaporated, the resulting residue was dissolved in methanol (20 ml), and then it was reacted with sodium borohydride (54 mg). The reaction solution was evaporated, and the reuslting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 119 mg of the free compound of the title compound as a white solid.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.71(m,2H), 2.04(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.00(ddd,J=12.8,10.0,3.0Hz,2H), 3.56(br-s,4H), 3.67(dt,J=12.8,4.4Hz,2H), 3.88(m,1H), 7.02(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(d,J=8.8Hz,2H).

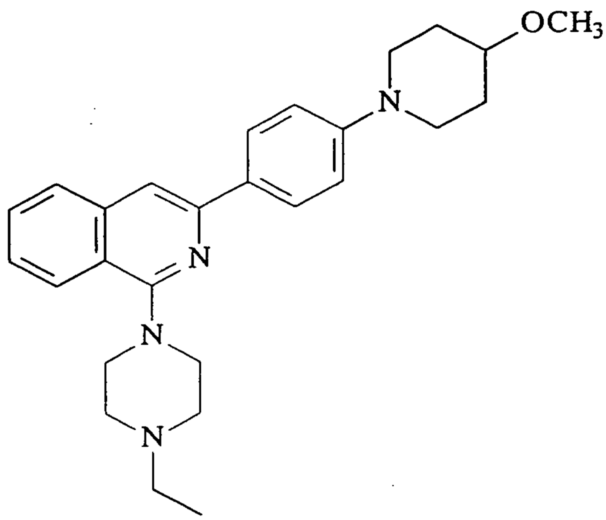
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 148 mg of the title compound as a white powder.

Hydrochloride:

m.p.; 178°C

MS(FAB) m/z 417$(M+H)^+$.

Example 98 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[4-(4-methoxypiperidin-1-yl)phenyl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.79 g) and 4-(4-methoxypiperidin-1-yl)phenyltributylstannum (1.30 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated, and ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.17 g of the free compound of the title compound as a yellow solid.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.72(m,2H), 2.03(m,2H), 2.55(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.00(ddd,J=12.8,10.0,3.0Hz,2H), 0.40(s,3H), 3.48(m,1H), 3.59(br-s,4H), 7.02(d,J=8.8Hz,2H), 7.41(br-t,1H), 7.55(br-

t,1H), 7.61(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.08(d,J=8.8Hz,2H).

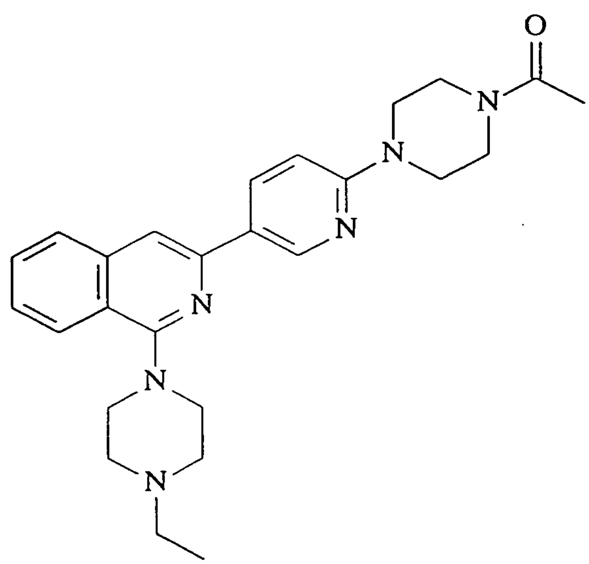
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.24 g of the title compound as a yellow powder.

Hydrochloride:

m.p.; 165°C

MS(FAB) m/z 431(M+H)$^+$.

Example 99 Synthesis of 3-[2-(4-acetylpiperazin-1-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.53 g) and [2-(4-acetylpiperazin-1-yl)pyridin-5-yl]tributylstannum (0.91 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated.

Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.67 g of the free compound of the tilte compound as a white powder.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.21(t,J=7.2Hz,3H), 2.16(s,3H), 2.81(br-s,4H), 3.56-3.66(m,8H), 3.73(m,2H), 3.78(m,2H), 6.75(d,J=8.8Hz,2H), 7.44(br-t,1H), 7.56(s,1H), 7.57(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.28(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.72 g of the title compound as a yellow powder.

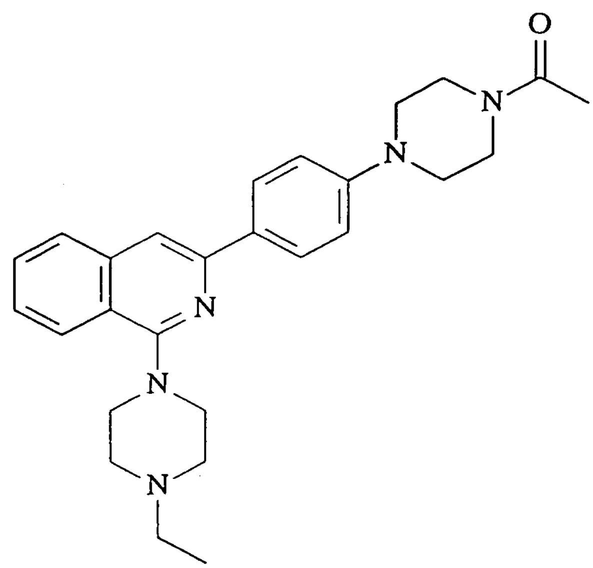
Hydrochloride:

m.p.; 206°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 2.08(s,3H), 3.23(m,2H), 3.37(m,2H), 3.54(br-t,2H), 3.61-3.69(m,6H), 3.77(br,2H), 3.86(br,2H), 3.98(br-d,2H), 7.42(m,1H), 7.63(br-t,1H), 7.77(br-t,1H), 7.97(br-d,1H), 8.11-8.16(m,2H), 8.65(m,1H), 8.79(br,1H).

Example 100 Synthesis of 3-[4-(4-acetylpiperazin-1-

yl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.27 g) and [4-(4-acetylpiperidin-1-yl)phenyl]tributylstannum (0.90 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.12 g of the free compound of the title compound as a white solid.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.21(t,J=7.2Hz,3H), 2.16(s,3H),

2.60(q,J=7.2Hz,2H), 2.81(br-s,4H), 3.26(m,4H), 3.62(br-s,4H), 3.65(m,2H), 3.81(m,2H), 7.02(d,J=8.8Hz,2H), 7.43(br-t,1H), 7.58(br-t,1H), 7.62(s,1H), 7.77(d,J=8.4Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=8.88Hz,2H).

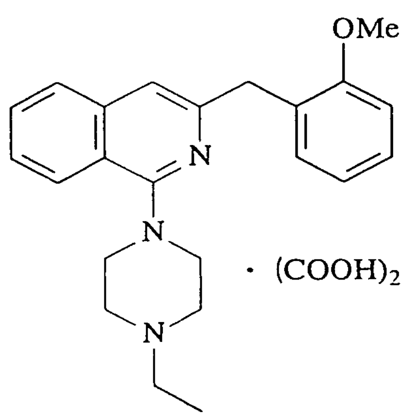
The resulting free compound form was converted into a hydrochloride in a conventional manner, recrystallized from ethanol/ether, to give 0.16 g of the title compound as a yellow powder.

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 2.07(s,3H), 3.22-3.28(m,4H), 3.51(br-t,2H), 3.60-3.68(m,4H), 3.98(br-d,2H), 7.17(m,1H), 7.56(br-t,1H), 7.71(br-t,1H), 7.94(br-d,1H), 7.94(br-d,1H), 7.98(br-s,1H), 8.07-8.13(m,2H).

MS(FAB) m/z 431 $(M+H)^+$.

Example 101 Synthesis of 3-(2-methoxybenzyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




Potassium hydroxide (117 mg) and hydrazine monohydrate (2 ml) were added to a solution of 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-

yl)isoquinoline (261 mg) in ethylene glycol (6 ml), and the resulting mixture was reacted at 140°C overnight. Water and ethyl acetate were added to the reaction solution, for partitioning. The resulting organic layer was washed with brine, dried and evaporated. The resulting residue was then purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (185 mg, yield; 73%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 194-197°C

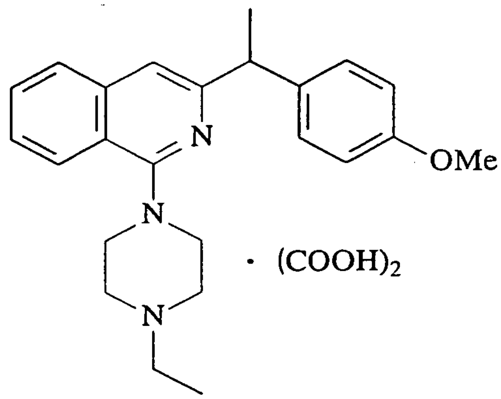
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(br,3H), 3.14(br,2H), 3.35(br,4H), 3.60(br,4H), 3.78(s,3H), 4.08(s,2H), 6.89(br,1H), 7.00(d,J=8.0Hz,1H), 7.09(s,1H), 7.17(d,J=8.0Hz,1H), 7.23(br,1H), 7.54(br,1H), 7.66(br,1H), 7.78(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H).

MS(FAB) m/z 374(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.53(q,J=7.2Hz,2H), 2.70(br,4H), 3.47(br,4H), 3.82(s,3H), 4.16(s,2H), 6.87-6.91(m,2H), 6.94(s,1H), 7.19-7.24(m,2H), 7.38(dt,J=8.0,0.8Hz,1H), 7.49(dt,J=8.0,0.8Hz,1H), 7.60(d,J=8.0Hz,1H), 8.01(d,J=8.0Hz,1H).

Example 102 Synthesis of 3-[α-methyl-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



3-[1-(4-Methoxyphenyl)ethen-1-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline obtained in Example 217 was converted into the hydrochloride. To the hydrochloride (145 mg) were added methanol (15 ml) and palladium/carbon catalyst (10 mg), and the resulting mixture was reacted in hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, which was then extracted with ethyl acetate. The resulting organic layer was washed with brine, dried and evaporated. Then, the residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (140 mg, yield; 96%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 86-88°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(t,J=7.2Hz,3H), 1.64(d,J=6.8Hz,3H), 3.13(br,2H), 3.35(br,4H), 3.60(br,4H),

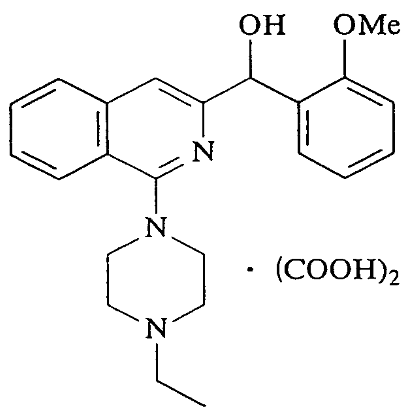
3.70(s,3H), 4.22(q,J=6.8Hz,1H), 6.84(d,J=8.4Hz,2H), 7.29(s,1H), 7.30(d,J=8.4Hz,2H), 7.54(t,J=8.0Hz,1H), 7.67(t,J=8.0Hz,1H), 7.82(d,J=8.0Hz,1H), 8.04(t,J=8.0Hz,1H).

MS(FAB) m/z 376$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.6Hz,3H), 1.70(d,J=7.2Hz,3H), 2.54(q,J=7.6Hz,2H), 2.71(br,4H), 3.48(br,4H), 3.77(s,3H), 4.18(q,J=7.2Hz,1H), 6.82(d,J=8.8Hz,2H), 7.00(s,1H), 7.36(d,J=8.8Hz,2H), 7.39(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.62(d,J=8.0Hz,1H), 8.00(d,J=8.4Hz,1H).

Example 103 Synthesis of 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




In the same manner as in Example 104, the free compound of the title compound was obtained (1.13 g, yield; 91%) from o-anisaldehyde (0.8 ml) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.05 g). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 100-103°C

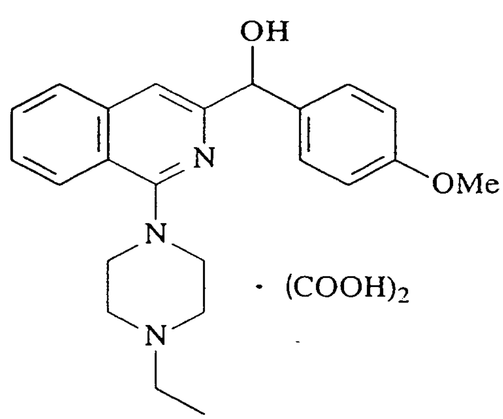
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 3.00(br,2H), 3.20(br,4H), 3.56(br,4H), 3.60(br,1H), 3.78(s,3H), 6.09(s,1H), 6.89(t,J=7.2Hz,1H), 6.97(d,J=7.2Hz,1H), 7.21(dt,J=7.6,2.0Hz,1H), 7.33(dd,J=7.6,2.0Hz,1H), 7.47(s,1H), 7.55(t,J=8.0Hz,1H), 7.68(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H).

MS(FAB) m/z 378(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.73(br,4H), 3.54(br,4H), 3.89(s,3H), 5.24(d,J=5.6Hz,1H), 6.23(d,J=5.6Hz,1H), 6.89-6.94(m,2H), 7.14(s,1H), 7.23(dt,J=7.2,1.6Hz,1H), 7.40(dd,J=7.2,1.6Hz,1H), 7.43(ddd,J=8.4,8.0,1.2Hz,1H), 7.54(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H).

Example 104 Synthesis of 3-[α-Hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




To a solution of 3-bromo-1-(4-ethylpiperazin-1-

yl)isoquinoline (1.08 g) in tetrahydrofuran (20 ml) was added 1.7 M t-butyl lithium (3.0 ml) at -78 °C, and the mixture was stirred for 15 min. Thereafter, p-anisaldehyde (0.82 ml) was added at -78 °C, and the mixture was stirred for 15 min. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated. Then, the residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (1.23 g, yield; 97%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 95-97°C

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.21(t,J=7.2Hz,3H), 3.02(br,2H), 3.23(br,4H), 3.46(br,4H), 3.60(t,J=6.8Hz,1H), 3.70(s,3H), 5.69(s,1H), 6.84(d,J=8.8Hz,2H), 7.36(d,J=8.8Hz,2H), 7.55(t,J=8.0Hz,1H), 7.58(s,1H), 7.69(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H).

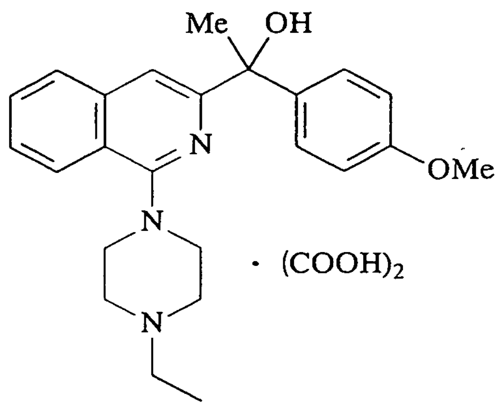
MS(FAB) m/z 378(M+H)$^+$.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.74(br,4H), 3.55(br,4H), 3.80(s,3H), 5.18(d,J=4.8Hz,1H), 5.72(d,J=4.8Hz,1H), 6.87(d,J=8.8Hz,2H), 7.00(s,1H), 7.35(d,J=8.8Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.0Hz,1H),

8.05(d,J=8.4Hz,1H).

Example 105 Synthesis of 3-[α-methyl-α-hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




To a solution of 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (667 mg) in tetrahydrofuran (10 ml) was added a 3.0 M solution of methylmagnesium bromide in diethyl ether (1.8 ml) at 0 °C. The mixture was reacted at 0°C for further 10 min, and then the reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was then extracted with ethyl acetate. The resulting organic layer was washed with water and brine, dried and evaporated. Then the resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system), to give a yellow oil (643 mg, yield; 92%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 179-181°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.20(t,J=7.6Hz,3H), 1.90(s,3H), 2.99(br,2H), 3.19(br,4H), 3.52(br,4H), 3.69(s,3H), 6.81(d,J=8.8Hz,2H), 7.48(d,J=8.8Hz,2H), 7.54(t,J=8.0Hz,1H), 7.66(s,1H), 7.67(t,J=8.0Hz,1H), 7.90(d,J=8.0Hz,1H), 8.02(d,J=8.0Hz,1H).

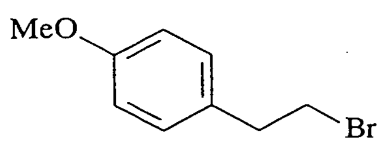
MS(FAB) m/z 392$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 1.95(s,3H), 2.53(q,J=7.2Hz,2H), 2.71(br,4H), 3.50(br,4H), 3.78(s,3H), 5.59(s,1H), 6.82(d,J=8.8Hz,2H), 7.15(s,1H), 7.43(d,J=8.8Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.69(d,J=8.0Hz,1H), 8.04(d,J=8.4Hz,1H).

Example 106 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline

(106-1) 4-Methoxyphenethyl bromide

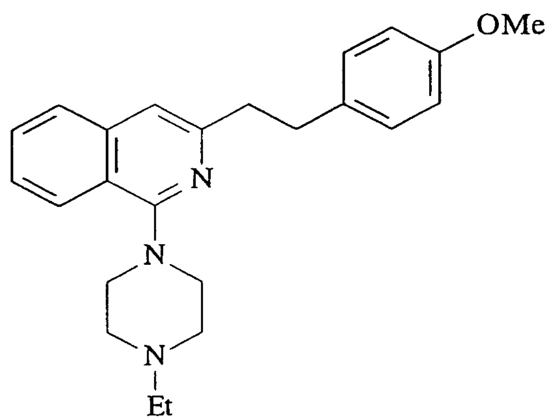


4-Methoxyphenethyl alcohol (50 g) and triphenylphosphine (103 g) were dissolved in methylene chloride (600 ml), followed by the addition of N-bromosuccinimide (70 g) in small portions under ice-cooling, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated, and to the resulting residue was added hexane. The insoluble matters were filtered off, while the resulting filtrate was

evaporated, to give the title compound as a colorless oil (50.32 g, yield; 71%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.10(2H,t,J=7.6Hz), 3.53(2H,t,J=7.6Hz), 3.80(3H,s), 6.86(2H,d,J=8.8Hz), 7.13(2H,d,J=8.8Hz).

(106-2) 1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyphenethyl)isoquinoline



Grignard reagent was prepared from magnesium (735 mg) and 4-methoxyphenethyl bromide (4.302 g) in a conventional manner. It was added dropwise into a solution of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (961 mg) and [1,3-bis(diphenylphosphino)propane]nickel (II) chloride (49 mg) in tetrahydrofuran (15 ml), in nitrogen atmosphere under ice-cooling. After stirring the resulting mixture for 10 min, it was further stirred at room temperature for 3.5 hr. To the resulting mixture was added 1N hydrochloric acid (10 ml), followed by stirring for 10 min. Then, the mixture was basified with a 5N sodium hydroxide. The insoluble matters were filtered off through Celite, and then the resulting filtrate was

extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated and purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale yellow crystals (346 mg, yield; 27%).

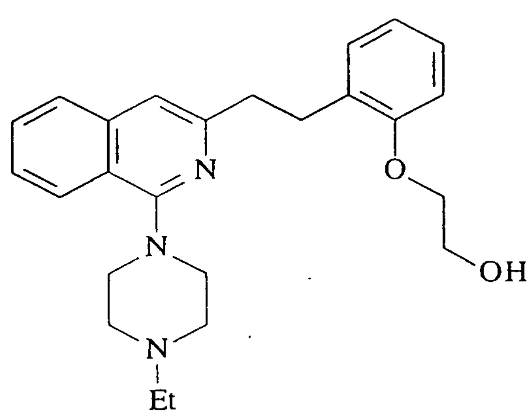
Hydrochloride:

m.p.; 224-227°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(3H,t,J=7.2Hz), 2.95-3.00(2H,m), 3.07-3.11(2H,m), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.31(1H,t,J=10.4Hz), 3.34(1H,t,J=10.4Hz), 3.59(2H,d,J=10.4Hz), 3.60(2H,t,J=12.8Hz), 3.08(3H,s), 3.95(2H,d,J=12.8Hz), 6.80(2H,d,J=8.8Hz), 7.14(2H,d,J=8.8Hz), 7.32(1H,s), 7.59(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz,), 7.84(1H,d,J=8Hz), 8.09(1H,d,J=8Hz), 11.43(1H,br-s).

ESI-Mass; 376($MH^+$).

Example 107 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenethyl]isoquinoline



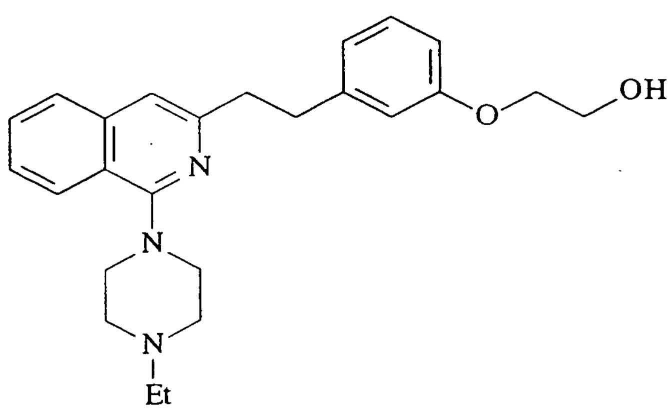
In the same manner as in Example 110, the oxalate of the title compound was obtained as a brown amorphous (209 mg, yield; 36%) from 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenylethynyl]isoquinoline (453 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 3.02(4H,s), 3.10(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.62(4H,m), 3.73(2H,t,J=5Hz), 3.98(2H,t,J=5Hz), 6.77(1H,ddd,J=7.6Hz,7.4Hz.1.2Hz), 6.92(1H,dd,J=8Hz,1.2Hz), 7.07(1H,dd,J=7.4Hz,1.6Hz), 7.10(1H,ddd,J=8Hz,7.6Hz,1.6Hz), 7.23(1H,s), 7.51(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.7(1H,dd,J=8Hz,1.2Hz), 8.03(1H,dd,J=8Hz,1.2Hz).

ESI-Mass; 406(MH$^+$).

Example 108 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)phenethyl]isoquinoline




In the same manner as in Example 110, the oxalate of the title compound was obtained as a colorless amorphous (218 mg, yield; 36%) from 1-(1-ethylpiperazin-4-yl)-3-[3-(2-

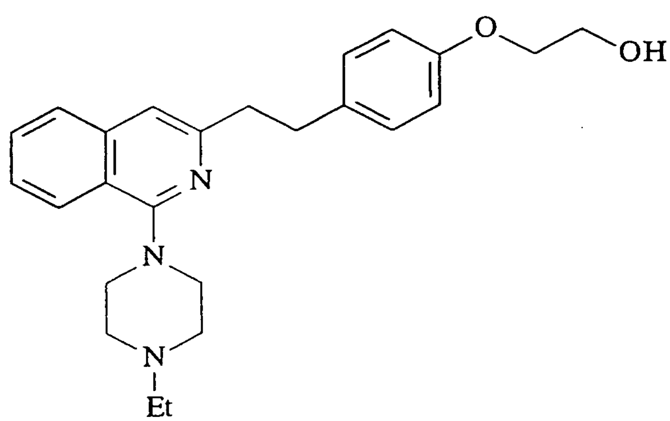
hydroxyethoxy)phenylethynyl]isoquinoline (454 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 3.00-3.04(4H,m), 3.09(2H,q,J=7.2Hz), 3.26-3.57(4H,m), 3.46-3.52(4H,m), 3.65(2H,t,J=5Hz), 3.89(2H,t,J=5Hz), 6.70(1H,dd,J=8Hz,2.5Hz), 6.76(1H,d,J=7.6Hz), 6.77(1H,d,J=2.5Hz), 7.12(1H,dd,J=8Hz,7.6Hz), 7.25(1H,s), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,d,J=8Hz), 8.04(1H,d,8Hz), 11.10(1H,br-s).

ESI-Mass; 406(MH$^+$).

Example 109 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenethyl]isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[trans-4-(2-hydroxyethoxy)styryl]isoquinoline (722 mg) was dissolved in ethanol (16 ml), to which was then added Lindlar catalyst (1.4 g). Then, the resulting mixture was stirred in hydrogen atmosphere for 2 days. After the catalyst was filtered off, the resulting solution was evaporated and purified by (NH)silica gel column chromatography (ethyl acetate/hexane

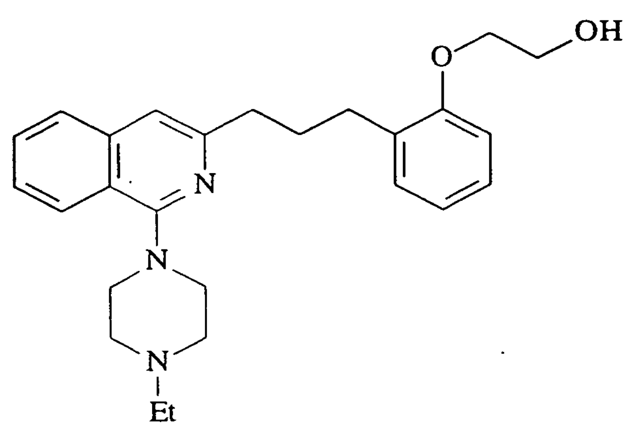
system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (118 mg, yield; 11%).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 2.99(2H,t,J=3.2Hz), 3.00(2H,t,J=3.2Hz), 3.10(2H,q,J=7.2Hz), 3.24-3.36(4H,m), 3.46-3.60(4H,m), 3.66(2H,t,J=5Hz), 3.89(2H,t,J=5Hz), 6.78(2H,d,J=8.8Hz), 7.09(2H,d,J=8.8Hz), 7.23(1H,s), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,d,J=8Hz), 8.04(1H,d,J=8Hz).

FAB-Mass; 406(MH$^+$).

Example 110 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-{3-[2-(2-hydroxyethoxy)phenyl]propyl}isoquinoline (619 mg) was converted into a hydrochloride, and then dissolved in ethanol (20 ml), to which was then added 10% palladium-carbon catalyst (1.25 g). The resulting mixture was stirred in hydrogen

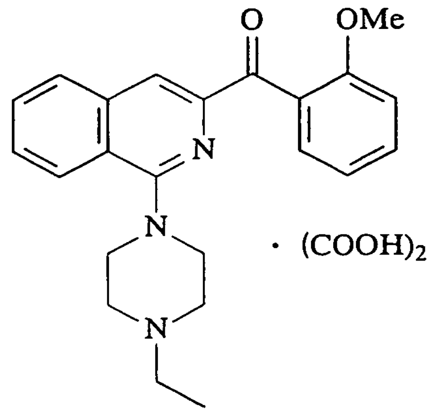
atmosphere overnight. After the catalyst was filtered off, the resulting solution was evapoareted. The reaction mixture was partitioned between ethyl acetate and 1N sodium hydroxide. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (200 mg, yield; 27%).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(3H,t,J=7.2Hz), 1.99(2H,qui,J=7.6Hz), 2.64(2H,t,J=7.6Hz), 2.76(2H,t,J=7.6Hz), 3.08(2H,q,J=7.2Hz), 3.26-3.34(4H,m), 3.42-3.60(4H,m), 3.68(2H,t,J=5.2Hz), 3.96(2H,t,J=5.2Hz), 6.84(1H,ddd,J=7.6Hz,7.4Hz,1.2Hz), 6.91(1H,dd,J=8Hz,1.2Hz), 7.12(1H,ddd,J=8Hz,7.6Hz,1.2Hz), 7.13(1H,dd,J=7.4Hz,1.6Hz), 7.26(1H,s), 7.51(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 420($MH^+$).

Example 111 Synthesis of 3-(2-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 112, the free compound of the title compound was obtained (600 mg, yield; 60%) from 3-[α-hydroxy-(2-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline (1.0 g) and manganese dioxide (1.2 g).

The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 153-156°C

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.20(t,J=7.2Hz,3H), 3.04(q,J=7.2Hz,2H), 3.22(br,4H), 3.42(br,4H), 3.63(s,3H), 7.08(t,J=8.0Hz,1H), 7.14(d,J=8.0Hz,1H), 7.43(dd,J=7.6,1.6Hz,1H), 7.54(dd,J=7.6,1.6Hz,1H), 7.78(t,J=7.6Hz,1H), 7.84(t,J=7.6Hz,1H), 8.16(d,J=7.6Hz,1H), 8.19(d,J=7.6Hz,1H).

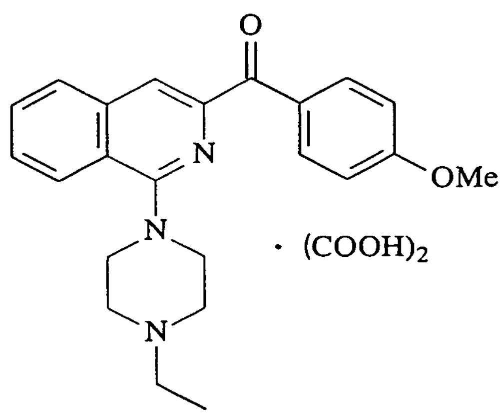
MS(FAB) m/z 376(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.12(t,J=7.2Hz,3H), 2.48(q,J=7.2Hz,2H), 2.62(br,4H), 3.36(br,4H), 3.69(s,3H),

6.96(d,J=8.4Hz,1H), 7.03(dt,J=7.6,0.8Hz,1H), 7.45(ddd,J=8.4,7.6,1.6Hz,1H), 7.55(dd,J=7.6,1.6Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.92(d,J=8.0Hz,1H), 8.06(s,1H), 8.09(d,J=8.4Hz,1H).

Example 112 Synthesis of 3-(4-methoxyphenylcarbonyl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



3-[α-Hydroxy-(4-methoxybenzyl)]-1-(4-ethylpiperazin-1-yl)isoquinoline (1.1 g) was dissolved in a mixture solution of benzene (20 ml) and methylene chloride (20 ml), followed by the addition of manganese dioxide (1.3 g). After the mixture was reacted under stirring at room temperature overnight, it was filtered and evaporated. The resulting crystals were washed with diethyl ether, to give the free compound of the title compound as a white solid (765 mg, yield; 70%). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 176-179°C

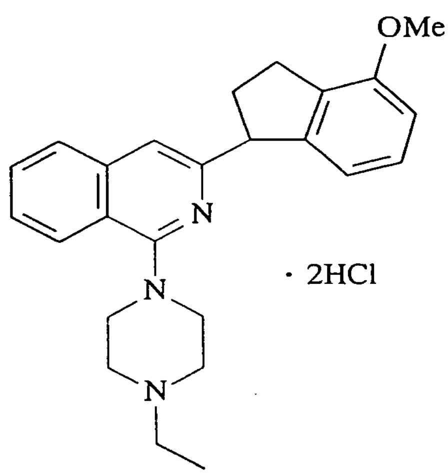
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.21(t,J=7.2Hz,3H), 3.01(br,2H), 3.24(br,2H), 3.59(br,6H), 3.87(s,3H), 7.08(d,J=8.8Hz,2H), 7.79(t,J=8.0Hz,1H), 7.84(t,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H), 8.13(s,1H), 8.17(d,J=8.0Hz,1H), 8.21(d,J=8.0Hz,1H).

MS(FAB) m/z 376(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.6Hz,3H), 2.54(q,J=7.6Hz,2H), 2.73(br,4H), 3.51(br,4H), 3.91(s,3H), 6.96(d,J=8.8Hz,2H), 7.62(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(ddd,J=8.4,8.0,1.2Hz,1H), 7.92(d,J=8.0Hz,1H), 8.06(s,1H), 8.14(d,J=8.4Hz,1H), 8.29(d,J=8.8Hz,2H).

Example 113 Synthesis of 3-(4-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manner as in Example 104, a yellow compound was obtained (440 mg, yield; 98%) from 5-methoxy-1-indanone (608 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). The resulting compound was converted into a

hydrochloride in a conventional manner, to give the title compound as white crystals.

Hydrochloride:

m.p.; 108-110°C

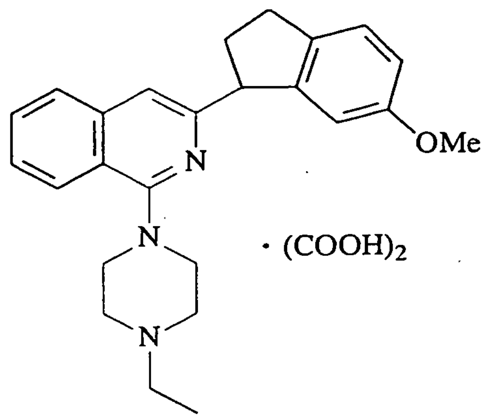
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.29(t,J=7.2Hz,3H), 2.39-2.46(m,1H), 2.48-2.82(m,1H), 2.83-2.89(m,1H), 2.99-3.07(m,1H), 3.14-3.24(m,4H), 3.40-3.58(m,4H), 3.76-3.90(m,2H), 3.80(s,3H), 4.58(t,J=7.2Hz,1H), 6.67(d,J=8.0Hz,1H), 6.79(d,J=8.0Hz,1H), 7.10(t,J=8.0Hz,1H), 7.30(s,1H), 7.58(t,J=8.4Hz,1H), 7.71(t,J=8.4Hz,1H), 7.86(d,J=8.4Hz,1H), 8.07(d,J=8.4Hz,1H).

MS(FAB) m/z 388(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.15(t,J=7.2Hz,3H), 2.17-2.61(m,2H), 2.51(q,J=7.2Hz,2H), 2.68(br,4H), 2.88-2.96(m,1H), 3.08-3.15(m,1H), 3.44(br,4H), 3.86(s,3H), 4.54(t,J=7.2Hz,1H), 6.70(d,J=7.6Hz,1H), 6.79(d,J=7.6Hz,1H), 7.02(s,1H), 7.10(t,J=7.6Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.02(d,J=8.4Hz,1H).

Example 114 Synthesis of 3-(6-methoxyindan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, an oil was obtained from 6-methoxy-1-indanone (713 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (937 mg). Methanol (20 ml) and platinum oxide (20 mg) were added to the oil (387 mg), and the mixture was reacted in hydrogen atmosphere overnight. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was purified by NH-silica gel column chromatography, to give a yellow oil (307 mg, yield; 79%). The oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 122-124°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(t,J=7.2Hz,3H), 2.34-2.42(m,1H), 2.44-2.54(m,1H), 2.82-2.93(m,1H), 3.02-3.10(m,4H), 3.30(br,4H), 3.53(br,5H), 3.64(s,3H), 4.48(t,J=7.2Hz,1H), 6.64(d,J=2.4Hz,1H), 6.74(dd,J=8.0,2.4Hz,1H), 7.19(d,J=8.0Hz,1H), 7.32(s,1H), 7.56(t,J=8.0Hz,1H), 7.69(t,J=8.0Hz,1H), 7.86(d,J=8.0Hz,1H),

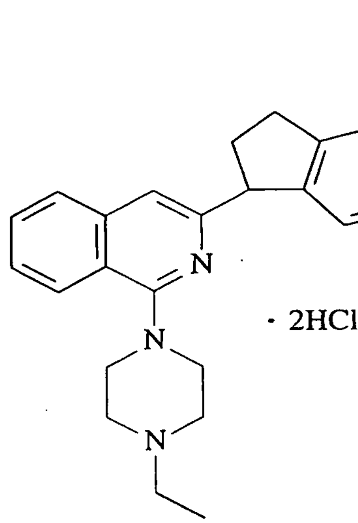
8.06(d,J=8.0Hz,1H).

MS(FAB) m/z 388$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.15(t,J=7.2Hz,3H), 2.41-2.61(m,2H), 2.52(q,J=7.2Hz,2H), 2.69(br,4H), 2.86-2.93(m,1H), 3.12-3.04(m,1H), 3.45(br,4H), 3.71(s,3H), 4.49(t,J=7.2Hz,1H), 6.72(d,J=2.4Hz,1H), 6.73(dd,J=8.0,2.4Hz,1H), 7.03(s,1H), 7.18(d,J=8.0Hz,1H), 7.41(ddd,J=8.4,8.0,1.2Hz,1H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 115 Synthesis of 3-[4-(2-hydroxyethoxy)indan-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manner as in Example 104, an oil was obtained from 5-(2-t-butyldimethylsilyloxyethoxy)-1-indanone (1.1 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (800 mg). To a solution of the oil in tetrahydrofuran (10 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in

tetrahydrofuran (6 ml), and the mixture was stirred at room temperature for 30 min. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give the free compound of the title compound as a colorless oil (394 mg, yield; 36%). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as a white amorphous.

Hydrochloride (amorphous):

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.28(t,J=7.2Hz,3H), 2.38-2.41(m,1H), 2.45-2.50(m,1H), 2.83-2.93(m,1H), 3.00-3.11(m,1H), 3.14-3.30(m,4H), 3.45-3.60(m,4H), 3.76(t,J=4.8Hz,2H), 3.82-3.91(m,1H), 4.03(br,2H), 4.58(t,J=7.2Hz,2H), 6.66(d,J=8.0Hz,1H), 6.78(t,J=8.0Hz,1H), 7.08(t,J=8.0Hz,1H), 7.28(s,1H), 7.58(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.86(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

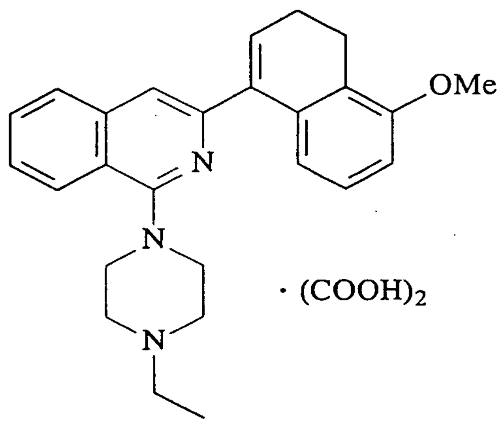
MS(FAB) m/z 418$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.45(t,J=7.2Hz,3H), 2.43-2.61(m,2H), 2.53(q,J=7.2Hz,2H), 2.69(br,4H), 2.89-2.97(m,1H), 3.09-3.17(m,1H), 3.44(br,4H), 3.99(t,J=4.0Hz,2H), 4.13-4.16(m,2H), 4.54(t,J=7.6Hz,1H), 6.71(d,J=7.6Hz,1H), 6.81(d,J=7.6Hz,1H), 7.03(s,1H), 7.09(t,J=7.6Hz,1H), 7.41(ddd,J=8.4,8.0,1.2Hz,1H), 7.53(ddd,J=8.4,8.0,1.2Hz,1H),

7.64(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 116 Synthesis of 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, a brown oil was obtained (97 mg, yield; 93%) from 5-methoxy-1-tetralone (711 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (860 mg). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 136-139°C

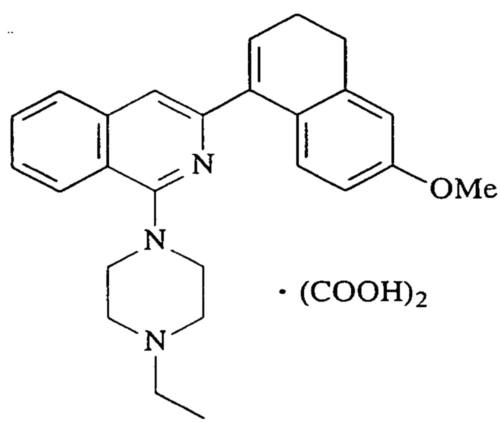
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(t,J=7.2Hz,3H), 2.36(br,2H), 2.77(t,J=8.0Hz,2H), 3.06(br,2H), 3.28(br,4H), 3.52(br,4H), 3.83(s,3H), 6.52(t,J=4.4Hz,1H), 6.79(d,J=8.0Hz,1H), 6.93(d,J=8.0Hz,1H), 7.11(t,J=8.0Hz,1H), 7.53(s,1H), 7.61(t,J=8.0Hz,1H), 7.72(t,J=8.4Hz,1H), 7.93(d,J=8.4Hz,1H), 8.12(d,J=8.4Hz,1H).

MS(FAB) m/z 400(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.40-2.45(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.88(t,J=8.0Hz,2H), 3.52(br,4H), 3.88(s,3H), 6.60(t,J=4.4Hz,1H), 6.82(d,J=8.0Hz,1H), 6.99(d,J=8.0Hz,1H), 7.09(t,J=8.0Hz,1H), 7.35(s,1H), 7.46(dt,J=8.4,1.2Hz,1H), 7.57(dt,J=8.4,1.2Hz,1H), 7.71(d,J=8.4Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 117 Synthesis of 3-(7-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




To a solution of 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (860 mg) in tetrahydrofuran (10 ml) was added 2.5 M n-butyl lithium (1.3 ml) at -78°C. Thereafter, the mixture was raised to -40°C, to which was then added 6-methoxy-1-tetralone (711 mg), and then the mixture was stirred at -40°C for 20 min. The reaction solution was poured into an aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The resulting organic layer was washed with

water and brine, dried and evaporated. Then, to the resulting residue were added methanol (10 ml) and 5N hydrochloric acid (1 ml), and the mixture was heated under reflux for 1 hr. The reaction solution was basified by adding a 2N aqueous solution of sodium hydroxide thereto, which was then partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give free compound of the title compound as a colorless oil (410 mg, yield; 86%). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 112-114°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(br,3H), 2.39(br,2H), 2.51(br,2H), 2.78(br,2H), 3.13(br,2H), 3.33(br,2H), 3.76(br,4H), 6.40(s,1H), 6.71(d,J=8.4Hz,1H), 6.87(s,1H), 7.14(d,J=8.4Hz,1H), 7.57(s,1H), 7.62(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.94(d,J=8.0Hz,1H), 8.12(d,J=8.0Hz,1H).

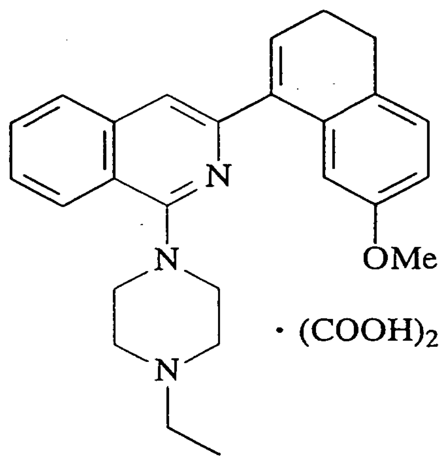
MS(FAB) m/z 400(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.42-2.47(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.85(t,J=7.6Hz,2H), 3.51(br,4H), 3.82(s,3H), 6.47(t,J=4.8Hz,1H), 6.67(dd,J=8.8,2.8Hz,1H), 6.79(d,J=2.8Hz,1H), 7.32(d,J=8.8Hz,1H), 7.44(s,1H),

7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.71(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 118 Synthesis of 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manner as in Example 104, the free compound of the title compound was obtained as a colorless oil (97 mg, yield; 98%) from 7-methoxy-1-tetralone and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline. The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 150-153°C

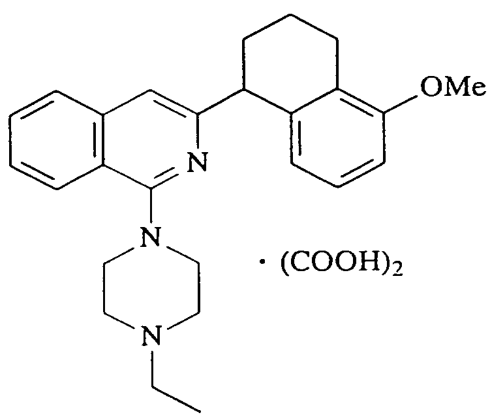
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(t,J=7.2Hz,3H), 2.38(br,2H), 2.74(t,J=7.6Hz,2H), 3.11(br,2H), 3.35(br,4H), 3.55(br,4H), 3.63(s,3H), 6.55(t,J=4.4Hz,1H), 6.78-6.79(m,2H), 7.18(d,J=8.4Hz,1H), 7.59(s,1H), 7.62(t,J=8.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.96(d,J=8.0Hz,1H), 8.13(d,J=8.0Hz,1H).

MS(FAB) m/z 400(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.42-2.47(m,2H), 2.54(q,J=7.2Hz,2H), 2.73(br,4H), 2.80(t,J=8.0Hz,2H), 3.52(br,4H), 3.70(s,3H), 6.60(t,J=4.8Hz,1H), 6.73(dd,J=8.0,2.8Hz,1H), 6.96(d,J=2.8Hz,1H), 7.13(d,J=8.0Hz,1H), 7.38(s,1H), 7.46(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.08(d,J=8.4Hz,1H).

Example 119 Synthesis of 3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




In the same manner as in Example 18, the free compound of the title compound was obtained as a colorless oil (218 mg, yield; 83%) from 3-(8-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (273 mg) and palladium/carbon catalyst (20 mg). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 133-136°C

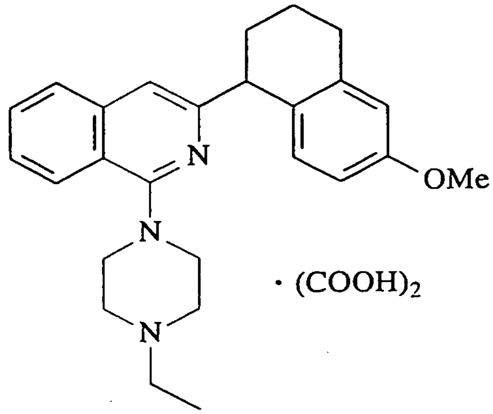
$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(t,J=7.2Hz,3H), 1.65-1.80(m,3H), 2.00(br,1H), 2.15(br,1H), 2.55-2.72(m,2H), 3.11(d,J=5.6Hz,2H), 3.32(br,2H), 3.54(br,1H), 3.60(br,2H), 3.80(s,3H), 3.93(br,2H), 4.24(t,J=5.6Hz,1H), 6.52(d,J=8.0Hz,1H), 6.79(d,J=8.0Hz,1H), 6.95(s,1H), 7.04(t,J=8.0Hz,1H), 7.55(t,J=8.0Hz,1H), 7.66(t,J=8.0Hz,1H), 7.78(d,J=8.0Hz,1H), 8.06(d,J=8.0Hz,1H).

MS(FAB) m/z 402$(M+H)^{+}$.

Free compound:

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.6Hz,3H), 1.68-1.75(m,2H), 2.01-2.09(m,1H), 2.23-2.29(m,1H), 2.53(q,J=7.6Hz,2H), 2.62-2.84(m,2H), 2.70(br,4H), 3.47(br,4H), 3.87(s,3H), 4.29(t,J=5.6Hz,1H), 6.67(d,J=8.0Hz,1H), 6.70(s,1H), 6.72(d,J=8.0Hz,1H), 7.06(t,J=8.0Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

<u>Example 120</u> <u>Synthesis of 3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate</u>



Methanol (30 ml) and platinum oxide (30 mg) were added to 3-(6-methoxy-1,2-dihydronapthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (347 mg), and the mixture was reacted in hydrogen atmosphere for 6 hr. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was purified by NH-silica gel column chromatography, to give the free compound of the title compound as an oil (189 mg, yield; 54%). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 170-173°C

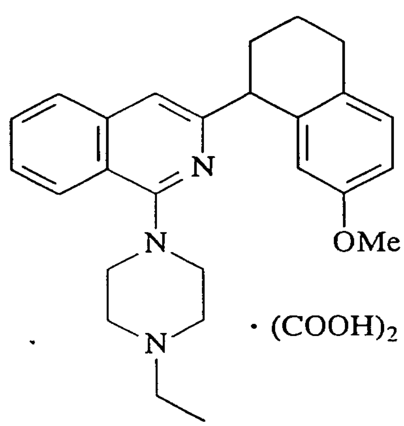
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.21(br,3H), 1.60-1.80(m,2H), 1.95-2.20(m,2H), 2.81(br,2H), 3.04(br,2H), 3.23(br,4H), 3.49(br,4H), 3.72(s,3H), 4.19(br,1H), 6.64(d,J=8.4Hz,1H), 6.73(s,1H), 6.82(d,J=8.4Hz,1H), 6.96(s,1H), 7.55(t,J=8.0Hz,1H), 7.65(t,J=8.0Hz,1H), 7.78(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H).

MS(FAB) m/z 402(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.05-2.14(m,3H), 2.18-2.26(m,1H), 2.51(q,J=7.2Hz,2H), 2.71(br,4H), 2.71-2.89(m,2H), 3.47(br,4H), 3.81(s,3H), 4.25(t,J=5.6Hz,1H), 6.66(dd,J=8.4,2.8Hz,1H), 6.70(d,J=2.8Hz,1H), 6.72(s,1H), 6.94(d,J=8.4Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.50(ddd,J=8.4,8.0,1.2Hz,1H), 7.57(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 121 Synthesis of 3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




In the same manner as in Example 18, the free compound of the title compound was obtained as a colorless oil (239 mg, yield; 61%) from 3-(6-methoxy-1,2-dihydronaphthalen-4-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (405 mg) and palladium/carbon catalyst (30 mg). The free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 110-112°C

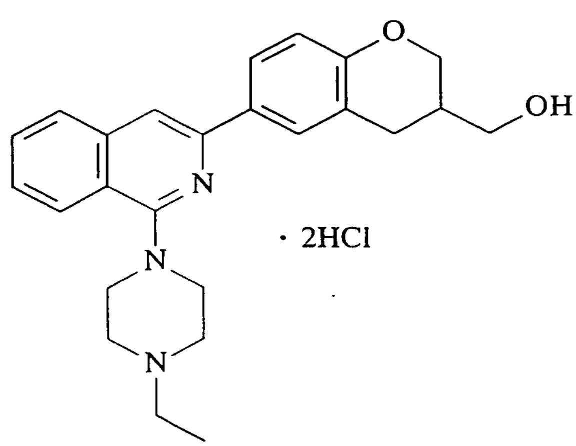
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.21(br,3H), 1.73(br,2H), 2.02(br,1H), 2.12(br,1H), 2.73(br,2H), 3.09(br,2H), 3.29(br,4H), 3.50(br,4H), 3.58(s,3H), 4.21(br,1H), 6.43(s,1H), 6.72(d,J=8.4Hz,1H), 6.97(s,1H), 7.06(d,J=8.4Hz,1H), 7.53(t,J=8.0Hz,1H), 7.64(t,J=8.0Hz,1H), 7.77(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H).

MS(FAB) m/z 402(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 1.66-1.81(m,2H), 2.05-2.13(m,1H), 2.21-2.28(m,1H), 2.52(q,J=7.2Hz,2H), 2.71(br,4H), 2.71-2.85(m,2H), 3.47(br,4H), 3.67(s,3H), 4.27(t,J=6.0Hz,1H), 6.58(d,J=2.4Hz,1H), 6.74(s,1H), 6.75(dd,J=8.8,2.4Hz,1H), 7.08(d,J=8.4Hz,1H), 7.41(dt,J=8.4,1.2Hz,1H), 7.51(dt,J=8.4,1.2Hz,1H), 7.59(d,J=8.4Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 122 Synthesis of 3-(3-hydroxymethylchroman-6-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 6-bromo-3-acetoxymethylchroman (4.67 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.2 g). To the resulting oil were added methanol (20 ml) and a 1N aqueous solution of sodium hydroxide (2 ml), and then reacted at 50°C for 2 hr. The reaction solution was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography, to give the free compound of the title compound as an oil. The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals (1.93 g, yield; 91%).

Hydrochloride:

m.p.; 168-172°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 2.13(br,1H), 2.63(dd,J=16.4,4.8Hz,1H), 2.89(dd,J=16.4,5.2Hz,1H), 3.19-3.26(m,2H), 3.33-3.43(m,3H), 3.48-3.60(m,3H), 3.62(d,J=11.6Hz,2H), 3.90-3.98(m,3H), 4.31(dd,J=11.2,2.0Hz,1H), 6.87(d,J=9.2Hz,1H), 7.56(t,J=8.0Hz,1H), 7.71(t,J=8.0Hz,1H), 7.91-7.96(m,4H), 8.09(d,J=8.0Hz,1H).

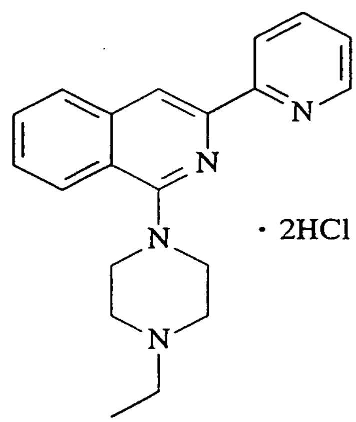
MS(FAB) m/z 404(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.30-2.36(m,1H), 2.56(q,J=7.2Hz,2H), 2.66-2.73(m,1H), 2.76(br,4H),

2.98(dd,J=16.4,1.2Hz,1H), 3.57(br,4H), 3.78-3.69(m,2H), 4.05-4.13(m,1H), 4.33-4.37(m,1H), 6.89(d,J=8.0Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(s,1H), 7.75(d,J=8.0Hz,1H), 7.88(dd,J=8.0,2.0Hz,1H), 7.89(s,1H), 8.05(d,J=8.4Hz,1H).

Example 123 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-(2-pyridyl)isoquinoline dihydrochloride or compound identified by the following analytical data and synthetic procedures



3-(2-Pyridyl)isoquinolin-1-one obtained by reacting N-methyl-o-toluamide (2.28 g) and 2-cyanopyridine (1.59 g) according to Example 10-1 was added to phosphorus oxychloride (10 ml), and the mixture was stirred at 100°C for 3 hr. The reaction solution was evaporated, and then ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water, an aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting 1-chloro-3-(2-pyridyl)isoquinoline was reacted with N-ethylpiperazine (15 ml) at 110°C for 12 hr. The reaction solution was evaporated,

and then ethyl acetate and water were added to the resulting residue. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=8.0Hz,3H), 2.57(q,J=8.0Hz,2H), 2.78(m,4H), 3.58(m,4H), 7.27(m,1H), 7.50(t,J=9.2Hz,1H), 7.61(t,J=9.2Hz,1H), 7.81(t,J=9.2Hz,1H), 7.89(d,J=9.2Hz,1H), 8.10(d,J=9.2Hz,1H), 8.40(s,1H), 8.52(d,J=9.2Hz,1H), 8.67(d,J=4.5Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.31 g of the title compound as a yellow powder.

Hydrochloride:

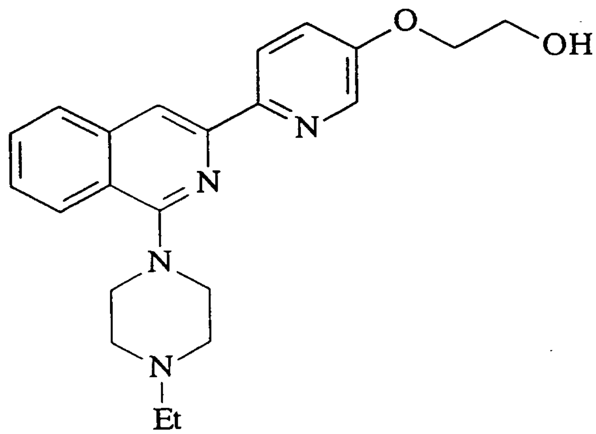
m.p.; 160-162°C

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.19-3.28(m,2H), 3.31-3.43(m,2H), 3.55-3.70(m,4H), 4.14(br-d,2H), 7.71-7.79(m,2H), 7.84(t,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.20(d,J=8.0Hz,1H), 8.30-8.39(m,1H), 8.63(s,1H), 8.66(d,J=8.0Hz,1H), 8.85(br-d,1H), 11.26(br-s,1H).

MS(FAB) m/z 319$(M+H)^+$.

<u>Example 124 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(2-</u>

hydroxyethoxy)pyridin-2-yl]isoquinoline



In the same manner as in Example 127-1, 5-(2-acetoxyethoxy)-2-tributylstannylpyridine was obtained as a colorless solid (3.362 g) from a mixture (4.015 g) of 2-iodo-3-hydroxypyridine and 4-iodo-3-hydroxypyridine, 2-bromoethyl acetate (4.551 g) and bis(tributyltin) (13.6 ml). The resulting compound and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (452 mg)were treated in the same manner as in Example 300, to give the hydrochloride of the title compound as yellow crystals (recrystallized from ethanol/isopropyl ether) (189 mg, yield; 29%).

Hydrochloride:

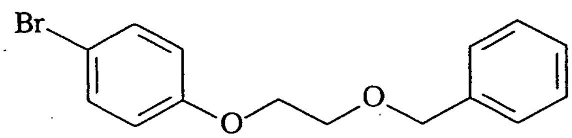
m.p.; 110-115°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.30-3.40(2H,m), 3.48-3.60(4H,m), 3.80-3.90(2H,m), 4.17(2H,d,J=13.2Hz), 4.30-4.40(2H,m), 7.75(1H,dd,J=8Hz,7Hz), 7.76-7.88(1H,m), 7.84(1H,dd,J=8H,7Hz), 8.07(1H,d,J=8Hz), 8.19(1H,d,J=8Hz), 8.16-8.30(1H,m), 8.44-8.60(2H,m).

ESI-Mass; 379($MH^+$).

Example 125 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline

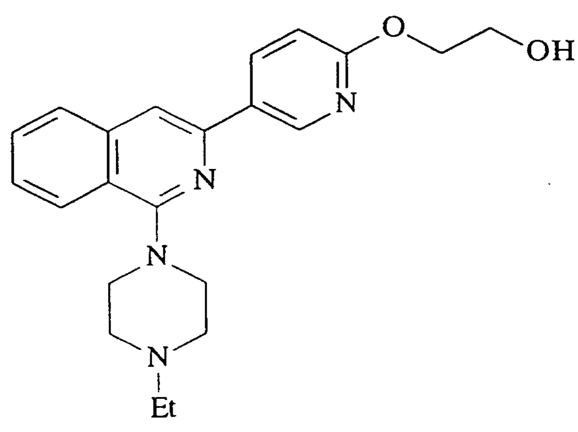
(125-1) 2-(2-Benzyloxyethoxy)-5-bromopyridine



In the same manner as in Example 126-1, 2.705 g of the title compound was obtained as a yellow oil from 2-benzyloxyethanol (15.219 g) and 2,5-dibromopyridine (2.369 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.81(2H,t,J=4.8Hz), 4.46(2H,t,J=4.8Hz), 4.61(2H,s), 6.72(1H,d,J=8.8Hz), 7.27-7.36(5H,m), 7.64(1H,dd,J=8.8Hz,2.4Hz), 8.16(1H,d,J=2.4Hz).

(125-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)pyridin-5-yl]isoquinoline



According to Example 167-2, 2-(2-benzyloxyethoxy)-5-bromopyridine (1.233 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg) were treated, which were continuously treated in the same manner as in Example 167-3,

to give the hydrochloride of the title compound. The resulting hydrochloride was recrystallized from ethanol/isopropyl ether, to give the title compound as pale yellow crystals (186 mg, yield; 27%).

Hydrochloride:

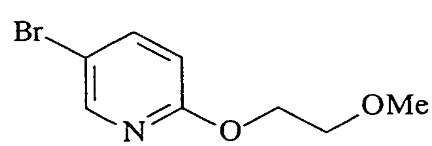
m.p.; 137-142°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.16-3.24(2H,m), 3.30(1H,t,J=10.4Hz), 3.33(1H,t,J=10.4Hz), 3.54(2H,t,J=13.6Hz), 3.58(2H,d,J=10.4Hz), 3.73(2H,t,J=5.2Hz), 3.99(2H,d,J=13.6Hz), 4.33(2H,t,J=5.2Hz), 6.96(1H,d,J=8.8Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 8.04(1H,s), 8.09(1H,d,J=8Hz), 8.46(1H,dd,J=8.8Hz,2.8Hz), 8.96(1H,d,J=2.8Hz), 11.15(1H,br-s).

ESI-Mass; 379($MH^+$).

Example 126 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline

(126-1) 2-(2-Methoxyethoxy)-5-bromopyridine

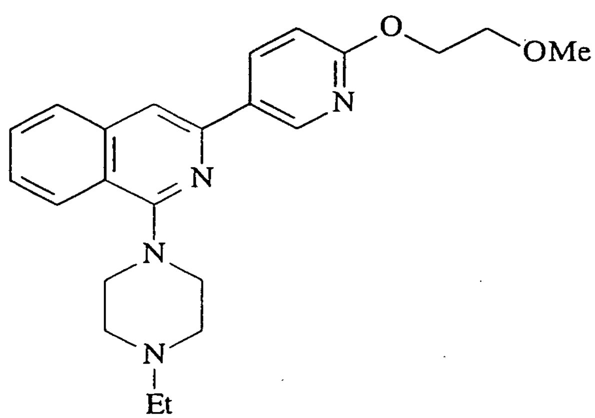



2-Methoxyethanol (7.9 mg) was dissolved in N,N-dimethylformamide (50 ml), followed the by addition of 60% sodium hydride (4 g) under ice-cooling, and the mixture was stirred for 20 min. Thereafter, it was stirred at 90°C for further 30 min. To the reaction mixture was added dropwise

2,5-dibromopyridine (2.369 g)/N,N-dimethylformamide (20 ml) solution, and the mixture was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (1.122 g, yield; 48%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.43(3H,s), 3.73(2H,t,J=4.6Hz), 4.44(2H,t,4.6Hz), 6.72(1H,dd,J=8.8Hz,0.8Hz), 7.64(1H,dd,J=8.8Hz,2.4Hz), 8.17(1H,dd,J=2.4Hz,0.8Hz).

(126-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-methoxyethoxy)pyridin-5-yl]isoquinoline




In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as yellow crystals (371 mg, yield; 53%) from 2-(2-methoxyethoxy)-5-bromopyridine (928 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg).

Hydrochloride:

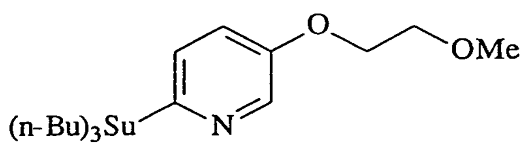
m.p.; 115-120°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(3H,t,J=7.2Hz), 3.18-3.65(2H,m), 3.70(2H,t,J=4.6Hz), 4.02(2H,d,J=13.6Hz), 4.45(2H,t,J=4.6Hz), 6.99(1H,d,J=8.4Hz), 7.61(1H,dd,J=8.4Hz,7Hz), 7.75(1H,dd,J=8.4Hz,7Hz), 7.96(1H,d,J=8.4Hz), 8.07(1H,s), 8.12(1H,d,J=8.4Hz), 8.48(1H,dd,J=8.4Hz,2.8Hz), 8.99(1H,s,J=2.8Hz).

ESI-Mass; 393($MH^+$).

Example 127 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline

(127-1) 5-Methoxyethoxy-2-tributylstannylpyridine

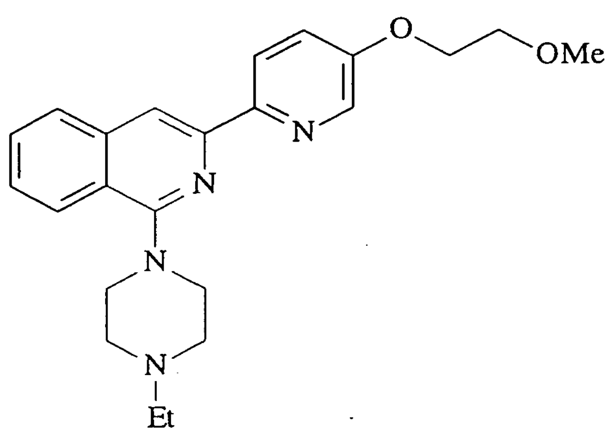


3-Hydroxypyridine (20.077 g) was dissolved in methanol (350 ml), sodium iodide (31.565 g) and sodium hydroxide (8.545 g) were added thereto, 5% sodium hypochlorite (314 mg) was added thereto under ice-cooling, and then the mixture was stirred for 5 hr. 10% sodium thiosulfate solution (200 ml) was added to the reaction mixture, which was then neutralized with 5N hydrochloric acid and extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a mixture of 2-iodo-3-hydroxypyridine and 4-iodo-3-hydroxypyridine (7:3) as a a yellow solid (12.544 g). The resulting mixture (2.97 g) was dissolved in N,N-

dimethylformamide (40 ml), followed by the addition of 2-bromoethyl methyl ether (3.822 g) and potassium carbonate (3.704 g), and the mixture was stirred at 80°C overnight. The resulting insoluble matters were filtered off. The resulting reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue and bis(tributyltin) (5 ml) were treated in the same manner as in Example 161-2, to give 1.142 g of the title compound as a colorless oil.

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.87(9H,t,J=7.4Hz), 1.11-1.16(6H,m), 1.29-1.37(6H,m), 1.50-1.61(6H,m), 3.43(3H,s), 3.74(2H,t,J=5Hz), 4.06(2H,t,J=5Hz), 6.97(1H,dd,J=8.4Hz,1.2Hz), 7.08(1H,dd,J=8.4Hz,4.8Hz), 8.37(1H,dd,J=4.8Hz,1.2Hz).

<u>(127-2) 1-(1-Ethylpiperazin-4-yl)-3-[5-(2-methoxyethoxy)pyridin-2-yl]isoquinoline</u>




In the same manner as in Example 161-3, the hydrochloride of the title compound was obtained as yellow crystals

(recrystallized form ethanol/isopropyl ether) (225 mg, yield; 36%) from 5-(2-methoxyethoxy)-2-tributylstannylpyridine (1.142 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (448 mg).

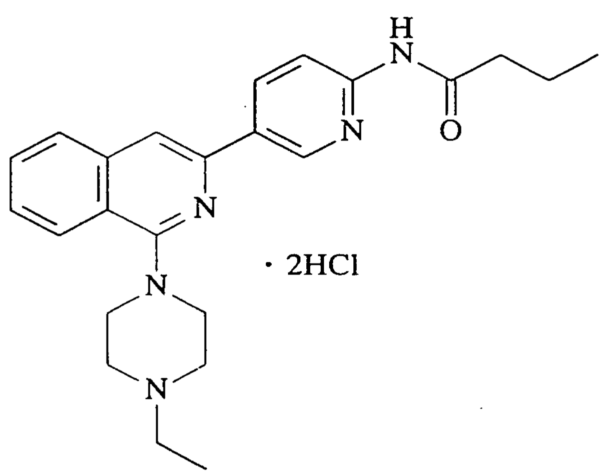
Hydrochloride:

m.p.; 116-119°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.15-3.25(2H,m), 3.30-3.40(2H,m), 3.37(3H,s), 3.54-3.62(4H,m), 3.80-3.85(2H,m), 4.20(2H,d,J=14Hz), 4.45-4.52(2H,m), 7.77(1H,dd,J=8Hz,7Hz), 7.86(1H,dd,J=8Hz,7Hz), 7.88-7.96(1H,m), 8.03(1H,d,J=8Hz), 8.20(1H,d,J=8Hz), 8.24-8.36(1H,m), 8.50-8.60(2H,m).

ESI-Mass; 393(MH$^+$).

<u>Example 128 Synthesis of 3-(2-propylcarbonylaminopyridin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound (338 mg, yield; 40%) from 5-bromo-2-propylcarbonylaminopyridine (3.11 g) and 3-

bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (514 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 168-171°C

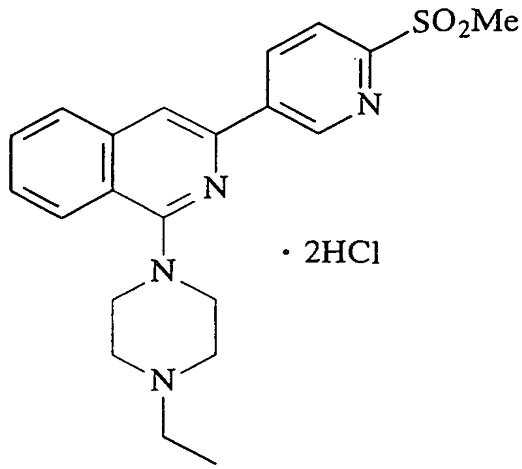
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.94(t,J=7.2Hz,3H), 1.35(t,J=7.2Hz,3H), 1.66(q,J=7.2Hz,2H), 2.47(t,J=7.2Hz,2H), 3.18-3.26(m,2H), 3.30-3.40(m,2H), 3.54-3.63(m,4H), 4.02(d,J=14.0Hz,2H), 7.64(t,J=8.0Hz,1H), 7.78(t,J=8.0Hz,1H), 7.99(d,J=8.0Hz,1H), 8.13,(d,J=8.8Hz,1H), 8.16(s,1H), 8.16(d,J=8.0Hz,1H), 8.69(dd,J=8.8,2.4Hz,1H), 9.14(d,J=2.4Hz,1H).

MS(FAB) m/z 404(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.04(t,J=7.2Hz,3H), 1.17(t,J=7.2Hz,3H), 1.76-1.85(m,2H), 2.42(t,J=7.2Hz,2H), 2.60(q,J=7.2Hz,2H), 2.76(br,4H), 3.56(br,4H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.61(ddd,J=8.4,8.0,1.2Hz,1H), 7.65(s,1H), 7.79(d,J=8.4Hz,1H), 8.07(d,J=8.4Hz,1H), 8.31(d,J=8.8Hz,1H), 8.44(dd,J=8.8,2.4Hz,1H), 9.06(br,1H).

Example 129 Synthesis of 3-[(2-methylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound (609 mg, yield; 82%) from 5-bromo-2-methylsulfonylpyridine (1.72 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (582 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 248-250°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.20-3.26(m,2H), 3.35(s,3H), 3.30-3.40(m,2H), 3.56-3.63(m,4H), 4.00(d,J=14.0Hz,2H), 7.71(t,J=8.0Hz,1H), 7.82(t,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,1H), 8.18(d,J=8.0Hz,1H), 8.37(s,1H), 8.86(dd,J=8.0,2.4Hz,1H), 9.57(d,J=2.4Hz,1H).

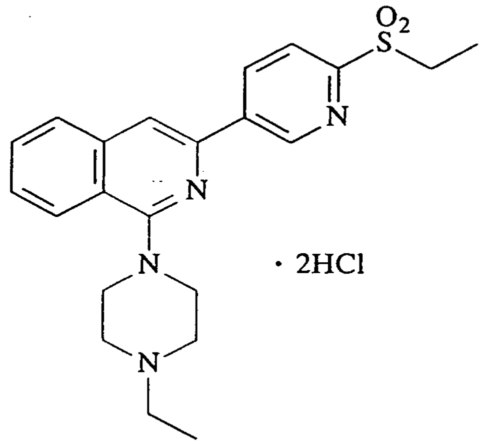
MS(FAB) m/z 397(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.8Hz,4H), 3.28(s,3H),

3.61(t,J=4.8Hz,4H), 7.56(t,J=8.0Hz,1H), 7.67(t,J=8.0Hz,1H), 7.79(s,1H), 7.85(d,J=8.0Hz,1H), 8.11(d,J=8.0Hz,1H), 8.17(d,J=8.0Hz,1H), 8.67(dd,J=8.0,2.0Hz,1H), 9.48(d,J=2.0Hz,1H).

Example 130 Synthesis of 3-[(2-ethylsulfonylpyridin)-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (710 mg, yield; 96%) from 5-bromo-2-ethylsulfonylpyridine (1.77 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (579 mg). The free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 155-159°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.35(t,J=7.2Hz,3H), 3.19-3.26(m,2H), 3.32-3.40(m,2H), 3.50(q,J=7.2Hz,2H), 3.59-3.66(m,4H), 4.07(d,J=13.2Hz,2H), 7.71(t,J=8.0Hz,1H), 7.83(t,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H),

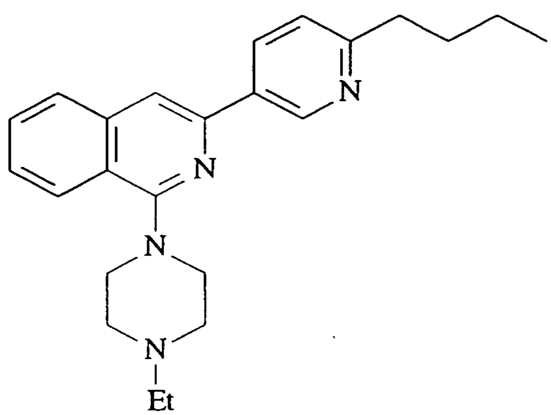
8.17(d,J=8.0Hz,1H), 8.19(d,J=8.4Hz,1H), 8.38(s,1H), 8.87(dd,J=8.4,2.0Hz,1H), 9.58(d,J=2.0Hz,1H).

MS(FAB) m/z 411$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.34(t,J=7.6Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(t,J=4.8Hz,4H), 3.45(q,J=7.6Hz,2H), 3.61(t,J=4.8Hz,4H), 7.56(ddd,J=8.4,8.0,1.2Hz,2H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.79(s,1H), 7.85(d,J=8.0Hz,1H), 8.11(d,J=8.4Hz,1H), 8.17(d,J=8.4Hz,1H), 8.67(dd,J=8.4,2.0Hz,1H), 9.49(d,J=2.0Hz,1H).

Example 131 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-butylpyridin-5-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline (148 mg) was dissolved in ethanol (20 ml), followed by the addition of platinum oxide (15 mg), and the mixture was stirred in hydrogen atmosphere at room temperature overnight. After the platinum oxide was filtered off, the resulting solution was evaporated, and the resulting residue

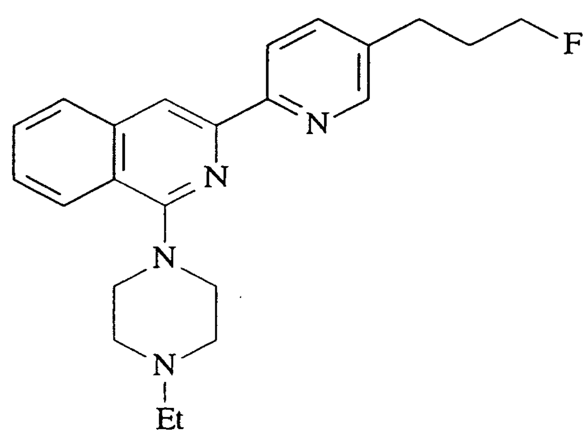
was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Continuously, the resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale brown amorphous (98 mg, yield; 50%).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.90(3H,t,J=7.2Hz), 1.24(3H,t,J=7.2Hz), 1.27-1.38(2H,m), 1.64-1.72(2H,m), 2.78(2H,t,J=7.6Hz), 3.12(2H,q,J=7.2Hz), 3.32-3.42(4H,brs), 7.36(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 375(MH$^+$).

Example 132 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-fluoropropyl)pyridin-2-yl)isoquinoline



Diethylaminosulfur trifluoride (237 ml) was dissolved in methylene chloride (2 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-

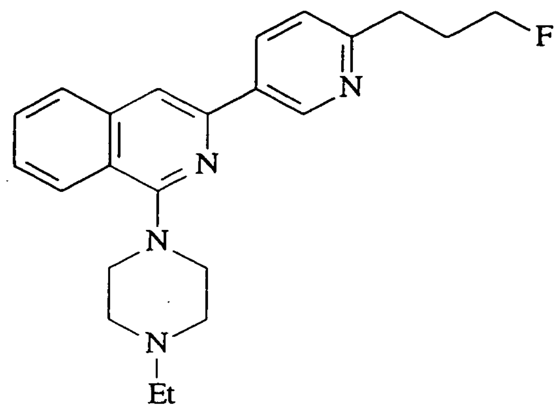
yl]isoquinoline (160 mg)/methylene chloride (2 ml) solution in nitrogen atmosphere at -70 °C. After the cooling bath was removed, subsequently, the resulting mixture was stirred for 2 hr. The reaction solution was diluted with methylene chloride, washed subsequently with an aqueous solution of saturated sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the oxalate of the title compound as a yellow amorphous (60 mg, yield; 31%).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.26(3H,t,J=7.2Hz), 1.94-2.10(2H,m), 2.76(2H,t,J=7.6Hz), 3.17(2H,q,J=7.2Hz), 3.35-3.48(4H,m), 3.60-3.80(4H,m), 4.43(1H,t,J=6Hz), 4.55(1H,t,J=6Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,dd,J=8Hz,2.4Hz), 8.07(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.34(1H,d,J=8Hz), 8.45(1H,s), 8.55(1H,d,J=2.4Hz).

ESI-Mass; 379($MH^+$).

Example 133 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-fluoropropyl)pyridin-5-yl]isoquinoline



Diethylaminosulfur trifluoride (53 ml) and pyridine hydrogen fluoride (320 ml) were dissolved in methylene chloride (3 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline (152 mg)/methylene chloride (2 ml) solution in nitrogen atmosphere at -70 °C. After the cooling bath was removed, subsequently, the resulting mixture was stirred for 2 hr. The reaction solution was diluted with methylene chloride, washed sequentially with an aqueous solution of sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (6 mg, yield; 5%).

Free compound:

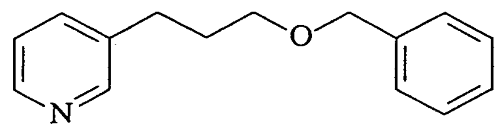
$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 2.15-2.28(2H,m), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 2.99(2H,t,J=7.6Hz), 3.60(4H,t,J=6.4Hz), 4.48(1H,t,J=6.4Hz), 4.60(1H,t,J=6.4Hz), 7.28(1H,d,J=8Hz), 7.49(1H,dd,J=8Hz,7Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.68(1H,s), 7.81(1H,d,J=8Hz),

8.09(1H,d,J=8Hz), 8.35(1H,dd,J=8Hz,2.4Hz), 9.30(1H,d,J=2.4Hz).

ESI-Mass; 379($MH^+$).

Example 134 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline

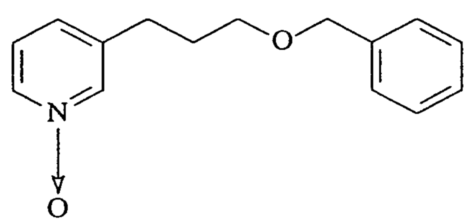
(134-1) 3-(3-Benzyloxypropyl)pyridine



In the same manner as in Example 167-1, the title compound was obtained as a brown oil (34.28 g, yield; 83%) from 3-pyridinepropanol (24.882 g) and benzyl bromide (26 ml).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.90-1.97(2H,m), 2.73(2H,t,J=7.8Hz), 3.48(2H,t,J=6.4Hz), 4.50(2H,s), 7.18(1H,dd,J=8Hz,4.8Hz), 7.27-7.37(5H,m), 7.48(1H,ddd,J=8Hz,2.4Hz,1.6Hz), 8.43(1H,dd,J=4.8Hz,1.6Hz), 8.45(1H,d,J=2.4Hz).

(134-2) 3-(3-Benzyloxypropyl)pyridine N-oxide

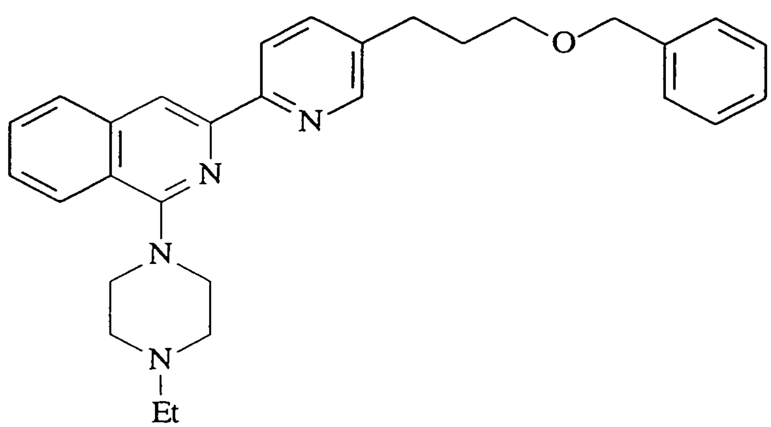


3-(3-Benzyloxypropyl)pyridine (34.28 g) was dissolved in acetic acid (260 ml), followed by the addition of a 30 % aqueous solution of hydrogen peroxide (52 ml), and the mixture was stirred at 50°C overnight. After cooling as it was, water (52

ml) was added to the reaction solution, which was then evaporated. The resulting residue was dissolved in chloroform, washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give the title compound as a yellow oil (30.23 g, yield; 88%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.87-1.95(2H,m), 2.70(2H,t,J=7.8Hz), 3.47(2H,t,J=6Hz), 4.50(2H,s), 7.08(1H,d,J=8Hz), 7.16(1H,dd,J=8Hz,6.4Hz), 7.28-7.39(5H,m), 8.05-8.10(2H,m).

(134-3) 1-(1-Ethylpiperazin-4-yl)-[5-(3-benzyloxypropyl)pyridin-2-yl]isoquinoline

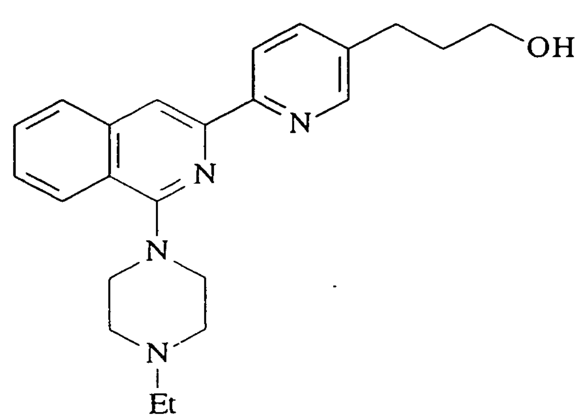


3-(3-Benzyloxypropyl)pyridine N-oxide (4.546 g) was dissolved in methylene chloride, phosphorus oxybromide (11.47 g) was added thereto under ice-cooling, and the mixture was stirred for 2 hr. Then, it was further stirred at room temperature for 2 hr. The reaction mixture was poured into warm water, and then it was neutralized by adding sodium bicarbonate thereto. The mixture was extracted with ethyl acetate. The

resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give a mixture of 2-bromo-5-(3-benzyloxypropyl)pyridine and 2-bromo-3-(3-benzyloxypropyl)pyridine (1:1) as a brown oil (2.203 g). The resulting mixture (1.111 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (662 mg) were treated in the same manner as in Example 167-2, to give the title compound as a yellow oil (326 mg, yield; 33%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 1.94-2.02(2H,m), 2.56(2H,q,J=7.2Hz), 2.77(4H,t,J=4Hz), 2.80(2H,t,J=7.2Hz), 2.80(2H,t,J=7.2Hz), 3.52(2H,t,J=6Hz), 3.59(4H,t,J=4Hz), 4.52(2H,s), 7.27-7.37(5H,m), 7.49(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.60(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,dd,J=8.4Hz,2.4Hz), 7.88(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.36(1H,s), 8.43(1H,dd,J=8.4Hz), 8.52(1H,d,J=2.4Hz).

<u>(134-4) 1-(1-Ethylpiperazin-4-yl)-3-[5-(3-hydroxypropyl)pyridin-2-yl]isoquinoline</u>



In the same manner as in Example 167-3, the oxalate of the title compound was obtained as a yellow amorphous (150 mg, yield; 43%) from 1-(1-ethylpiperazin-4-yl)-3-[5-(3-benzyloxypropyl)pyridin-2-yl]isoquinoline (326 mg).

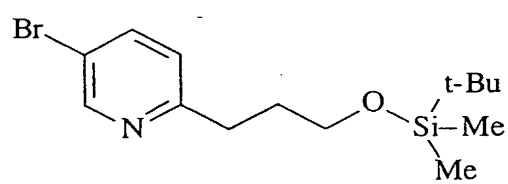
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(3H,t,J=7.2Hz), 1.72-1.80(2H,m), 2.69(2H,t,J=7.8Hz), 3.11(2H,q,J=7.2Hz), 3.30-3.40(4H,m), 3.44(2H,t,J=6.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz), 8.06(1H,d,J=8Hz), 8.12(1H,d,J=8.4Hz), 8.33(1H,d,J=8Hz), 8.43(1H,s), 8.53(1H,d,J=2.4Hz).

ESI-Mass; 377($MH^+$).

Example 135 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline

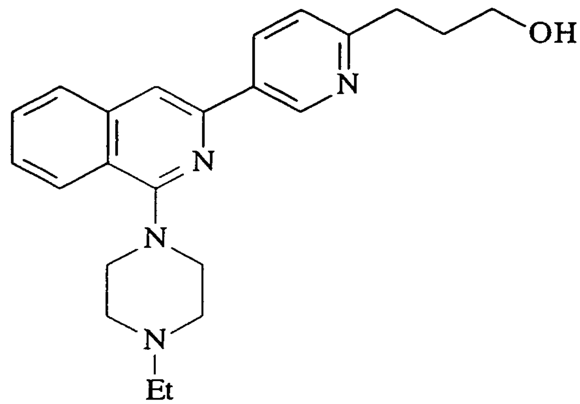
(135-1) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)propyl]pyridine




From 5-bromo-2-pyridinepropanol (4.266 g) synthesized according to J. O. C., 53, 386, 1988, the title compound was obtained as a colorless oil in the same manner as in Example 163-1 (6.297 g, yield; 97%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.04(6H,s), 0.90(9H,s), 1.89-1.97(2H,m), 2.82(2H,t,J=7.8Hz), 3.65(2H,t,J=6.2Hz), 7.07(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(135-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the free compound of the title compound was obtained as a yellow solid (1.288 g, yield; 94%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxypropyl]pyridine (2.973 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (1.158 g). A part (150 mg) of the resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a pale yellow amorphous (80 mg, yield; 43%).

Oxalate:

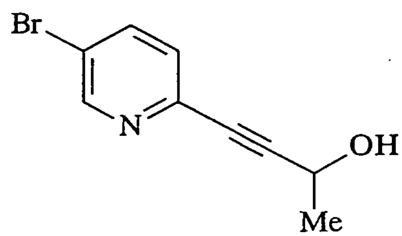
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 1.80-1.84(2H,m), 2.81(2H,t,J=7.6Hz), 3.15(2H,q,J=7.2Hz), 3.34-3.46(4H,m), 3.45(2H,t,J=6.4Hz), 3.60-3.80(4H,m), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass; 377(MH$^+$).

Example 136 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-

hydroxybutyl)pyridin-5-yl]isoquinoline

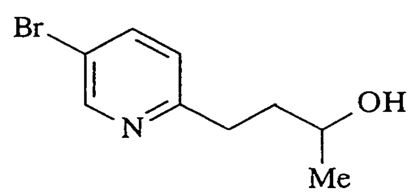
(136-1) 5-Bromo-2-(3-hydroxy-1-butynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (15.895 g, yield; 88%) from 2,5-dibromopyridine (18.951 g) and 3-butyn-2-ol (6.3 ml).

$^1$H-NMR(400MHz,CDCl$_3$); $\delta$ (ppm) 1.57(3H,d,J=6.8Hz), 4.77(1H,m), 7.31(1H,d,J=7.8Hz), 7.79(1H,dd,J=7.8Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

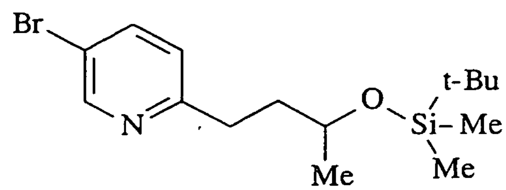
(136-2) 5-Bromo-2-(3-hydroxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.783 g, yield; 60%) from 5-bromo-2-(3-hydroxy-1-butyryl)pyridine (4.521 g).

$^1$H-NMR(400MHz,CDCl$_3$); $\delta$ (ppm) 1.23(3H,d,J=6Hz), 1.78-1.93(2H,m), 2.91(2H,t,J=7.8Hz), 3.23(1H,br-s), 3.78-3.88(1H,m), 7.09(1H,d,J=8.4Hz), 7.73(1H,dd,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

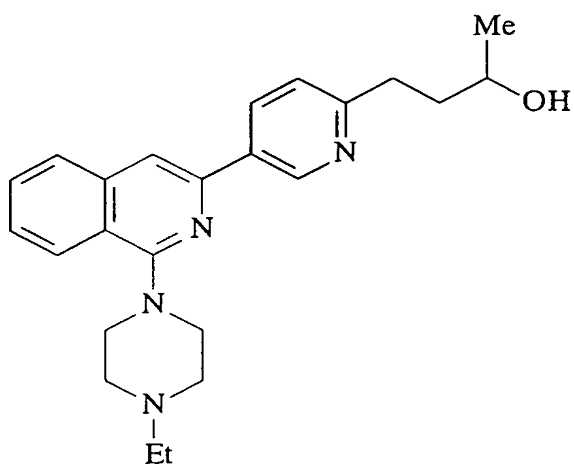
(136-3) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)butyl]pyridine



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (3.75 g, yield; 95%) from 5-bromo-2-(3-hydroxybutyl)pyridine (2.647 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.04(6H,s), 0.88(9H,s), 1.16(3H,d,J=6Hz), 1.77-1.83(2H,m), 2.67-2.87(2H,m), 3.56-3.58(1H,m), 7.04(1H,d,J=8.4Hz), 7.69(1H,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

(136-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxybutyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (420 mg, yield; 56%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxybutyl]pyridine (2.066 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (491 mg).

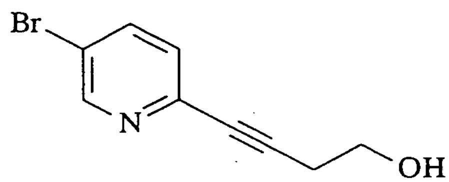
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.09(3H,d,J=6Hz), 1.24(3H,t,J=7.2Hz), 1.70-1.78(2H,m), 2.74-2.90(2H,m), 3.13(2H,q,J=7.2Hz), 3.37(4H,br-s), 3.60-3.76(6H,m), 7.37(2H,d,J=8.4Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.39(1H,dd,J=8.4Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 391($MH^+$).

Example 137 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline

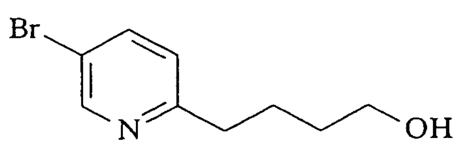
(137-1) 5-Bromo-2-(4-hydroxy-1-butynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (6.6 g, yield; 48%) from 2,5-dibromopyridine (14.213 g) and 3-butyn-1-ol (4.5 ml).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.72(2H,t,J=6.4Hz), 3.85(1H,t,J=6.4Hz), 3.86(1H,t,J=6.4Hz), 7.29(1H,d,J=8.4Hz), 7.77(1H,dd,J=8.4Hz,2.4Hz), 8.60(1H,d,J=2.4Hz).

(137-2) 5-Bromo-2-(4-hydroxybutyl)pyridine

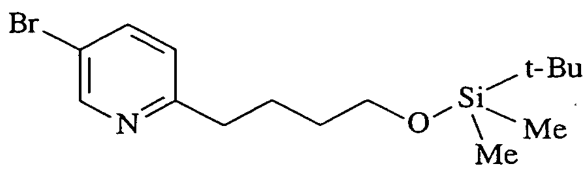


In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (3.397 g, yield; 74%) from 5-

bromo-2-(4-hydroxy-1-butynyl)pyridine (4.522 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.61-1.67(2H,m), 1.77-1.85(3H,m), 2.80(2H,t,J=7.6Hz), 3.68(2H,m), 7.07(1H,d,J=8Hz), 7.72(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

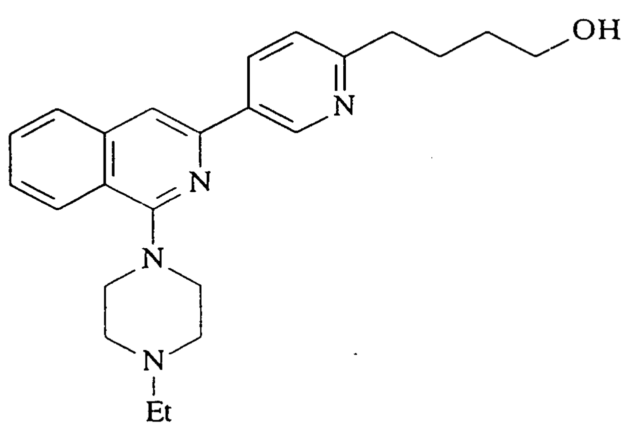
(137-3) 5-Bromo-2-[4-(t-butyldimethylsilyloxy)butyl]pyridine



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (2.484 g, yield; 87%) from 5-bromo-2-(4-hydroxybutyl)pyridine (1.905 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.04(6H,s), 0.88(9H,s), 1.52-1.60(2H,m), 1.72-1.79(2H,m), 2.76(2H,t,J=7.6Hz), 3.63(2H,t,J=6.6Hz), 7.06(1H,d,J=8Hz), 7.70(1H,dd,J=8Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(137-4) Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-hydroxybutyl)pyridin-5-yl]isoquinoline



In the same manner as in Example 167-2, the oxalate of the

title compound was obtained as a yellow amorphous (420 mg, yield; 64%) from 5-bromo-2-[4-(t-butyl)dimethylsilyloxybutyl]pyridine (2.484 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (435 mg).

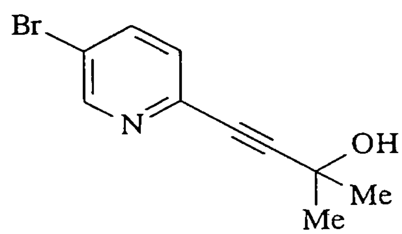
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 1.42-1.49(2H,m), 1.68-1.76(2H,m), 2.78(2H,t,J=7.6Hz), 3.15(2H,q,J=7.2Hz), 3.36-3.44(4H,br-s), 3.41(2H,t,J=6.2Hz), 7.36(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass; 391(MH$^+$).

Example 138 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline oxalate

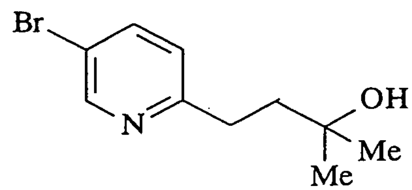
(138-1) 5-Bromo-2-(3-methyl-3-hydroxy-1-butynyl)pyridine




In the same manner as in Example 139-1, the title compound was obtained as a yellowish brown solid (17.91 g, yield; 94%) from 2,5-dibromopyridine (18.951 g) and 2-methyl-3-butyn-2-ol (6.3 ml).

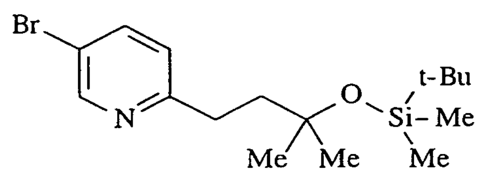
$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.64(6H,s), 2.16(1H,br-s), 7.31(1H,d,J=8.4Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

(138-2) 5-Bromo-2-(3-methylbutane-3-hydroxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (1.366 g, yield; 28%) from 5-bromo-2-(3-methyl-3-hydroxy-1-butynyl)pyridine (4.802 g).
$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.29(6H,s), 1.73(1H,s), 1.90(2H,t,J=7.8Hz), 7.09(1H,d,J=8.4Hz), 7.71(1H,dd,J=8.4Hz,2.4Hz), 8.55(1H,d,J=2.4Hz).

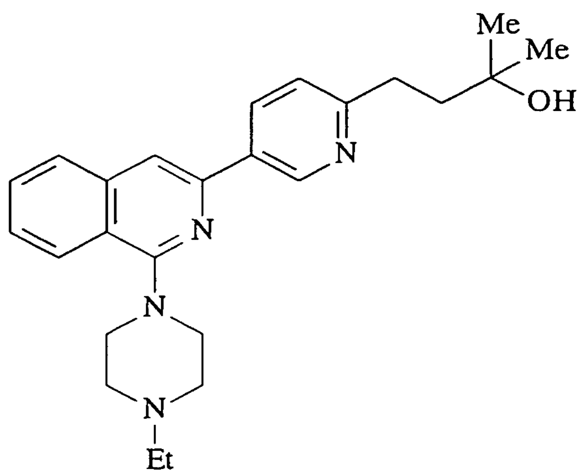
(138-3) 5-Bromo-2-[3-(t-butyldimethylsilyloxy)-3-methylbutyl]pyridine



5-Bromo-2-(3-methylbutane-3-hydroxybutyl)pyridine (1.359 g) was dissolved in methylene chloride (20 ml), followed by the sequential addition of 2,6-lutidine (2.5 ml) and t-butyldimethylsilyltrifluoromethanesulfonic acid (1.7 ml) in nitrogen atmosphere under ice-cooling, and the mixture was stirred overnight. The reaction mixture was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (1.724 g, yield; 86%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.10(6H,s), 0.88(9H,s), 1.27(6H,s), 1.78-1.83(2H,m), 2.82-2.87(2H,m), 7.06(1H,d,J=8.4Hz), 7.69(1H,dd,J=8.4Hz,2.4Hz), 8.56(1H,d,J=2.4Hz).

(138-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxy-3-methylbutyl)pyridin-5-yl]isoquinoline oxalate




In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (132 mg, yield; 30%) from 5-bromo-2-[3-(t-butyl)dimethylsilyloxy-3-methylbutyl]pyridine (1.724 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (324 mg).

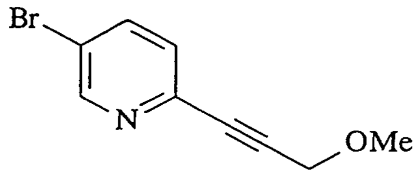
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.15(6H,s), 1.25(3H,t,J=7.2Hz), 1.74-1.79(2H,m), 2.80-2.85(2H,m), 3.13(2H,q,J=7.2Hz), 3.32-3.42(4H,br-s), 3.58-3.78(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.10(1H,s), 8.11(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.25(1H,d,J=2.4Hz).

ESI-Mass; 405($MH^+$).

Example 139 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate

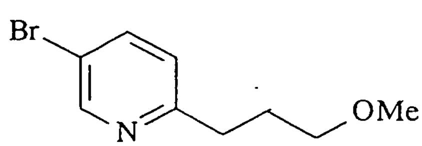
(139-1) 5-Bromo-2-(3-methoxypropynyl)pyridine



2,5-Dibromopyridine (16.582 g) was dissolved in triethylamine (200 ml), followed by the addition of methyl propargyl ether (5.9 ml), copper iodide (267 mg) and bis(triphenylphosphine)palladium (II) chloride (46 mg). The resulting mixture was stirred in nitrogen atmosphere at room temperature for 1 hr. Subsequently, it was stirred at room temperature for further 3 hr. After the resulting insoluble matters were filtered off, the resulting solution was evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown solid (12.411 g, yield; 79%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.47(3H,d,J=0.8Hz), 4.34(2H,s), 7.34(1H,d,J=8Hz), 7.79(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 8.64(1H,d,J=2.4Hz).

(139-2) 5-Bromo-2-(3-methoxypropyl)pyridine

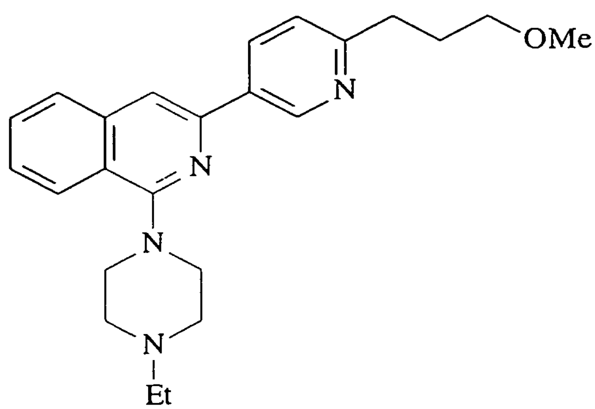


5-Bromo-2-(3-methoxypropynyl)pyridine (5.652 g) was

dissolved in ethanol (150 ml), followed by the addition of triethylamine (2.5 ml) and platinum oxide (230 mg), and the resulting mixture was stirred in hydrogen atmosphere at room temperature for 5 hr. After the platinum oxide was filtered off, the resulting mixture was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (3.991 g, yield; 68%).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.95-2.03(2H,m), 2.82(2H,t,J=7.6Hz), 3.34(3H,s), 3.41(2H,t,J=6.4Hz), 7.07(1H,d,J=8Hz), 7.71(1H,dd,J=8Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

<u>(139-3) Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate</u>




In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (982 mg, yield; 74%) from 5-bromo-2-(3-methoxypropyl)pyridine (2.301

g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (865 mg).

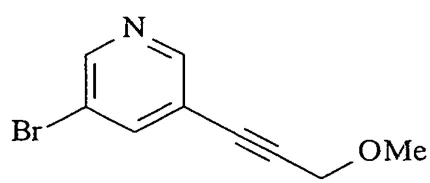
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(3H,t,J=7.2Hz), 1.88-1.97(2H,m), 2.81(2H,t,J=7.6Hz), 3.13(2H,q,J=7.2Hz), 3.23(3H,s), 3.32-3.42(6H,m), 3.60-3.80(4H,m), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 8.11(1H,s), 8.40(1H,dd,J=8Hz,2.4Hz), 9.27(1H,d,J=2.4Hz).

ESI-Mass; 391($MH^+$).

Example 140 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate

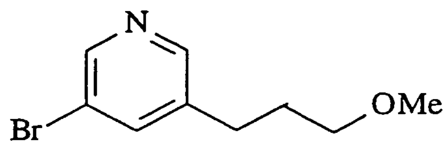
(140-1) 5-Bromo-3-(3-methoxypropynyl)pyridine



In the same manner as in Example 139-1, the title compound was obtained as a yellowish orange solid (7.216 g, yield; 64%) from 3,5-dibromopyridine (11.854 g) and methyl propargyl ether (4.2 ml).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.46(3H,s), 4.33(2H,s), 7.89(1H,t,J=2Hz), 8.58(1H,d,J=2Hz), 8.61(1H,d,J=2Hz).

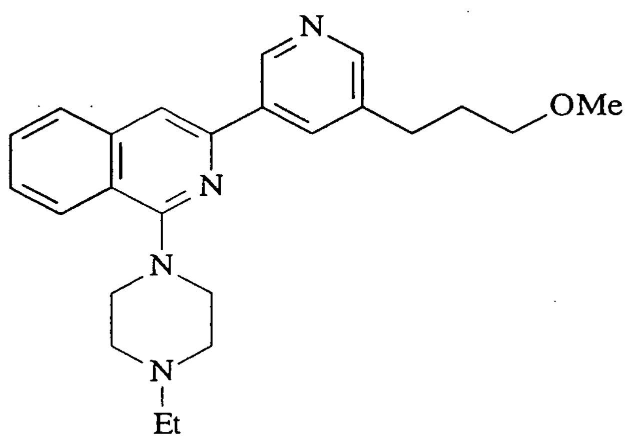
(140-2) 5-Bromo-3-(3-methoxypropyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a pale yellow oil (3.62 g, yield; 79%) from 5-bromo-3-(3-methoxypropynyl)pyridine (4.521 g).

$^1$H-NMR(400MHz,$CDCl_3$); δ (ppm) 1.85-1.92(2H,m), 2.70(2H,t,J=7.8Hz), 3.35(3H,s), 3.38(2H,t,J=6.2Hz), 7.67(1H,t,J=2Hz), 8.37(1H,d,J=2Hz), 8.51(1H,d,J=2Hz).

(140-3) 1-(1-Ethylpiperazin-4-yl)-3-[3-(3-methoxypropyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellow amorphous (324 mg, yield; 64%) from 5-bromo-3-(3-methoxypropyl)pyridine (1.151 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (345 mg).

Oxalate:

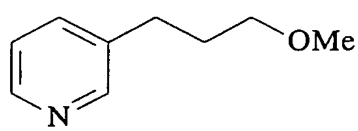
$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.25(3H,t,J=7.2Hz), 1.84-1.92(2H,m), 2.73(2H,t,J=7.6Hz), 3.16(2H,q,J=7.2Hz),

3.25(3H,s), 3.36(2H,t,6.4Hz), 3.38-3.48(4H,m), 3.60-3.80(4H,m), 7.63(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8.4Hz,7Hz,1.2Hz), 7.98(1H,d,J=8.4Hz), 8.12(1H,d,J=8.4Hz), 8.17(1H,m), 8.33(1H,t,J=2.4Hz), 8.43(1H,t,J=2.4Hz), 8.45(1H,d,J=2.4Hz), 9.21(1H,d,J=2.4Hz).

ESI-Mass; 391($MH^+$).

Example 141 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline oxalate

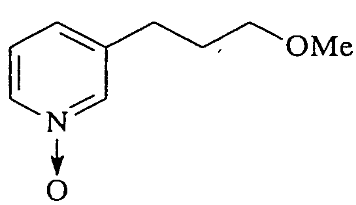
(141-1) 3-(3-Methoxypropyl)pyridine



In the same manner as in Example 167-1, the title compound was obtained as a yellow oil (5.494 g, yield; 72%) from 3-pyridinepropanol (6.452 g) and methyl iodide (3.4 ml).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.86-1.93(2H,m), 2.70(2H,t,J=7.8Hz), 3.35(3H,s), 3.39(2H,t,J=6.2Hz), 7.21(1H,dd,J=8Hz,4.8Hz), 7.51(1H,dt,J=8Hz,1.6Hz), 8.45(1H,dd,J=4.8Hz,1.6Hz), 8.46(1H,d,J=1.6Hz).

(141-2) 3-(3-Methoxypropyl)pyridine N-oxide

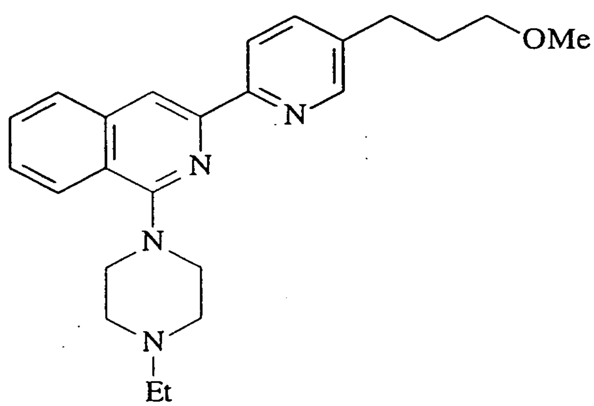


3-(3-Methoxypropyl)pyridine (5.551 g) was dissolved in methylene chloride (60 ml), followed by the addition of 70%

m-perbenzoic acid (10.86 g) and stirring under ice-cooling for 90 min. The reaction mixture was washed sequentially with a 10% aqueous solution of sodium sulfite and an aqueous solution of saturated sodium bicarbonate, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/methanol system), to give the title compound as a yellow oil (5.901 g, yield; 95%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.85-1.92(2H,m), 2.69(2H,t,J=7.6Hz), 3.35(3H,s), 3.39(2H,t,J=6.2Hz), 7.14(1H,d,J=7.2Hz), 7.21(1H,dd,J=7.2Hz,6.8Hz), 8.08-8.12(2H,m).

(141-3) 1-(1-Ethylpiperazin-4-yl)-3-[5-(3-methoxypropyl)pyridin-2-yl]isoquinoline oxalate




In the same manner as in Example 134-3, the oxalate of the title compound was obtained as a brown amorphous (120 mg, yield; 9%) from 3-(3-methoxypropyl)pyridine N-oxide (5.901 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (694 mg).

Oxalate:

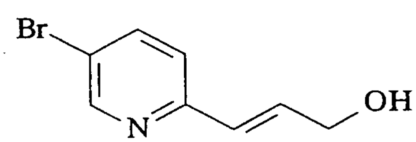
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 1.80-

1.88(2H,m), 2.69(2H,t,J=7.2Hz), 3.15(2H,q,J=7.2Hz), 3.24(3H,s), 3.34(2H,t,J=6.2Hz), 3.34-3.46(4H,m), 3.58-3.80(4H,m), 7.26(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,dd,J=8.4Hz,2.4Hz,), 8.07(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.33(1H,d,J=8.4Hz), 8.44(1H,s), 8.53(1H,d,J=2.4Hz).

ESI-Mass; 391($MH^+$).

Example 142 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline oxalate

(142-1) 5-Bromo-2-(3-hydroxy-1-propenyl)pyridine

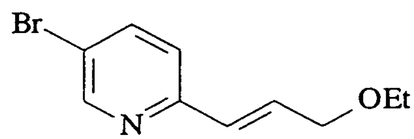


3-(5-Bromo-2-pyridinyl)-3-propyn-1-ol (10.602 g) synthesized according to J. O. C., 53, 386, 1988 was dissolved in tetrahydrofuran (100 ml), to which were then added lithium aluminum hydride (1.06 g) in several portions under ice-cooling, and then the mixture was stirred for 10 min. Water (1.1 ml), 5N sodium hydroxide (1.1 ml) and water (3.3 ml) were sequentially added to the reaction mixture, and the resulting insoluble matters were filtered off through Celite. The resulting filtrate was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (3.718 g, yield; 34%).

$^1H$-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.66(1H,br-s), 4.38(2H,br-s),

6.68(1H,dt,J=15.6Hz,5Hz), 7.18(1H,d,8.4Hz), 7.74(1H,dd,J=8.4Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

(142-2) 5-Bromo-2-(3-ethoxy-1-propenyl)pyridine

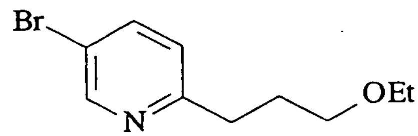


5-Bromo-2-(3-hydroxy-1-propenyl)pyridine (3.718 g) was dissolved in tetrahydrofuran (60 ml), followed by the sequential addition of triethylamine (7.1 ml) and methanesulfonyl chloride (1.6 ml) under ice-cooling, and the resulting mixture was stirred as it was, for 25 min. After the resulting insoluble matters were filtered off, the mixture was evaporated. The resulting residue was dissolved in ethanol (60 ml), followed by the addition of sodium ethoxide (1.388 g)/ethanol (25 ml) solution under ice-cooling, and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (2.607 mg, yield; 65%).

$^1H$-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 3.56(2H,q,J=7.2Hz), 4.17(2H,dd,J=5.2Hz,1.6Hz), 6.65(1H,dt,J=15.8Hz,1.6Hz), 6.79(1H,dt,J=15.8Hz,5.2Hz), 7.16(1H,d,J=8.4Hz), 7.71(1H,dd,J=8.4Hz,2.4Hz),

8.58(1H,d,J=2.4Hz).

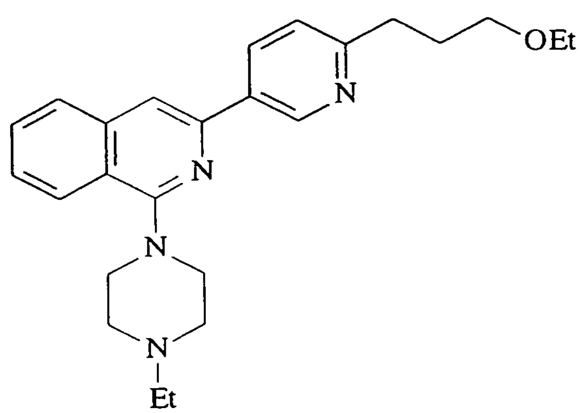
(142-3) 5-Bromo-2-(3-ethoxypropyl)pyridine



The title compound was obtained as a brown oil (2.286 g, yield; 74%) from 5-bromo-2-(3-ethoxy-1-propenyl)pyridine (3.079 g) in the same manner as in Example 139-2.

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(3H,t,J=7.2Hz), 1.96-2.03(2H,m), 2.83(2H,t,J=7.8Hz), 3.45(2H,t,J=6Hz), 3.47(2H,q,J=7.2Hz), 7.08(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.58(1H,d,J=2.4Hz).

(142-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-ethoxypropyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (472 mg, yield; 91%) from 5-bromo-2-(3-ethoxypropyl)pyridine (1.465 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (348 mg).

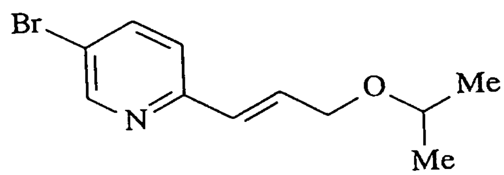
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.10(3H,t,J=7.2Hz), 1.25(3H.t,J=7.2Hz), 1.88-1.96(2H,m), 2.82(2H,t,J=7.6Hz), 3.13(2H,q,J=7.2Hz), 3.36-3.43(8H,m), 3.58-3.80(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.41(1H,dd,,J=8Hz,2.4Hz), 9.27(1H,d,J=2.4Hz).

ESI-Mass; 405($MH^+$).

Example 143 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline oxalate

(143-1) 5-Bromo-2-[3-(2-propoxy)-1-propenyl]pyridine

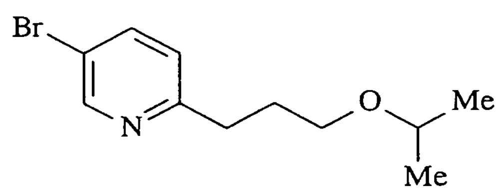


5-Bromo-2-(3-hydroxy-1-propenyl)pyridine (8.891 g) was dissolved in tetrahydrofuran (200 ml), followed by the sequential addition of triethylamine (17.6 ml) and methanesulfonyl chloride (3.9 ml) under ice-cooling, and the mixture was stirred for 20 min. After the resulting insoluble matters were filtered off, the solution was evaporated. The resulting residue was dissolved in 2-propanol (100 ml), sodium 2-propanoxide/2-propanol solution prepared from 60% sodium hydride (2 g) and 2-propanol (70 ml) was added thereto under ice-cooling, and the resulting mixture was stirred, as it was, at room temperature for 30 min. After the resulting insoluble

matters were filtered off from the reaction mixture, the resulting solution was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown oil (3.519 g, yield; 33%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.22(6H,d,J=6Hz), 3.69(1H,sept,J=6Hz), 4.18(2H,dd,J=5.2Hz,1.6Hz), 6.66(1H,dd,J=15.8Hz,1.6Hz), 6.79(1H,dd,J=15.8Hz,5.2Hz), 7.19(1H,d,J=8.4Hz), 7.73(1H,dd,J=8.4Hz,2.4Hz), 8.59(1H,d,J=2.4Hz).

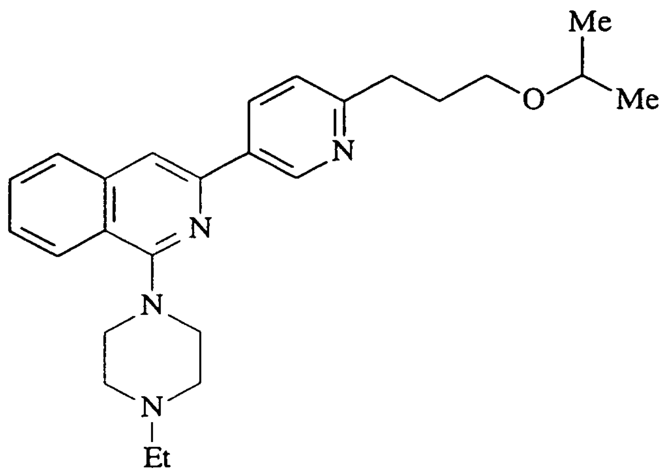
(143-2) 5-Bromo-2-[3-(2-propoxy)propyl]pyridine



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.859 g, yield; 81%) from 5-bromo-2-[3-(2-propoxy)-1-propenyl]pyridine (3.519 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.14(6H,d,J=6Hz), 1.94-2.01(2H,m), 2.83(2H,t,J=7.8Hz), 3.43(2H,t,J=6Hz), 3.54(1H,sept,J=6Hz), 7.08(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.57(1H,d,2.4Hz).

(143-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-[3-(2-propoxy)propyl]pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (418 mg. yield; 73%) from 5-bromo-2-[3-(2-propoxy)propyl]pyridine (1.291 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (348 mg).

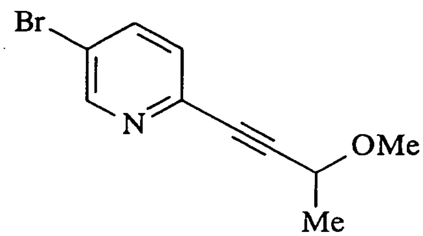
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.07(3H,t,J=6Hz), 1.25(3H.t,J=7.2Hz), 1.86-1.96(2H,m), 2.82(2H,t,J=7.6Hz), 3.14(2H,q,J=7.2Hz), 3.33-3.43(4H,m), 3.38(2H,t,J=6.4Hz), 3.50(1H,qui,J=6Hz), 7.37(1H,d,J=8Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.11(1H,d,J=8Hz), 8.41(1H,dd,J=8Hz,2.4Hz), 9.27(1H,d,2.4Hz).

ESI-Mass; 419(MH$^+$).

Example 144 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline oxalate

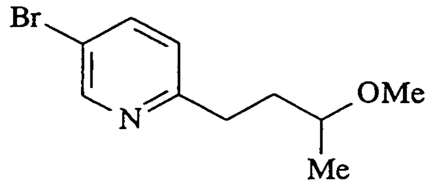
(144-1) 5-Bromo-2-(3-methoxy-1-butynyl)pyridine



5-Bromo-2-(3-hydroxy-1-butynyl)pyridine (5.426 g) was dissolved in tetrahydrofuran (60 ml), followed by the sequential addition of triethylamine (10 ml) and methanesulfonyl chloride (2.2 ml) under ice-cooling, and the resulting mixture was stirred for 1 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in methanol (16 ml), and under ice-cooling, 28% sodium methoxide/methanol solution (4.6 ml) was added thereto and the resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown oil (1.968 g, yield; 34%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.54(3H,d,J=6.4Hz), 3.85(1H,t,J=6.4Hz), 3.86(1H,t,J=6.4Hz), 7.33(1H,dd,J=8.4Hz,0.8Hz), 7.79(1H,dd,J=8.4Hz,2.4Hz), 8.64(1H,dd,J=2.4Hz,0.8Hz).

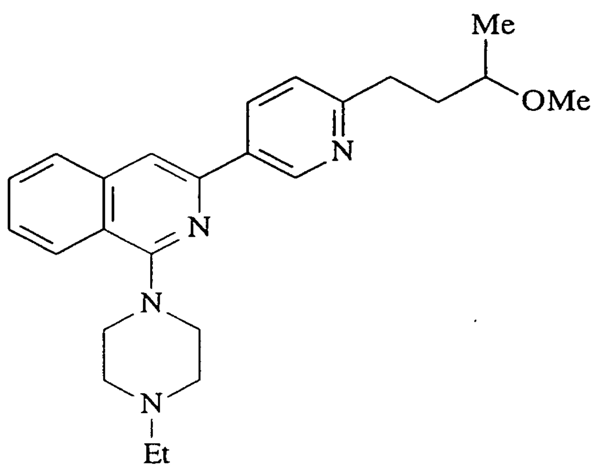
(144-2) 5-Bromo-2-(3-methoxybutyl)pyridine



In the same manner as in Example 139-2, the title compound was obtained as a brown oil (1.125 g, yield; 56%) from 5-bromo-2-(3-methoxy-1-butynyl)pyridine (1.968 g).

$^1$H-NMR(400MHz,CDCl$_3$); $\delta$ (ppm) 1.17(3H,d,J=6.4Hz), 1.83-1.90(2H,m), 3.32(4H,s), 7.07(1H,d,J=8.4Hz), 7.70(1H,dd,J=8.4Hz,2.4Hz), 8.57(1H,d,J=2.4Hz).

(144-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-methoxybutyl)pyridin-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a yellowish brown amorphous (352 mg, yield; 58%) from 5-bromo-2-(3-methoxybutyl)pyridine (1.125 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (377 mg).

Oxalate:

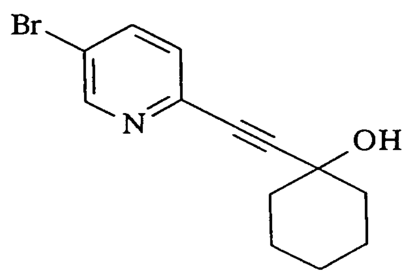
$^1$H-NMR(400MHz,DMSO-d$_6$); $\delta$ (ppm) 1.11(3H,d,J=6.4Hz),

1.24(3H,t,J=7.2Hz), 1.75-1.90(2H,m), 2.74-2.87(2H,m), 3.13(2H,q,J=7.2Hz), 3.22(3H,s), 3.26-3.34(1H.m), 3.32-3.42(4H,br-s), 7.37(1H,d,J=8Hz), 7.61(1H,dd,J=8Hz,7Hz), 7.74(1H,dd,J=8Hz,7Hz), 7.96(1H,d,J=8Hz), 8.11(1H,s), 8.12(1H,d,J=8Hz), 8.41(1H,dd,J=8Hz,2.4Hz), 9.26(1H,d,J=2.4Hz).

ESI-Mass; 405($MH^+$).

Example 145 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-{2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl}isoquinoline oxalate

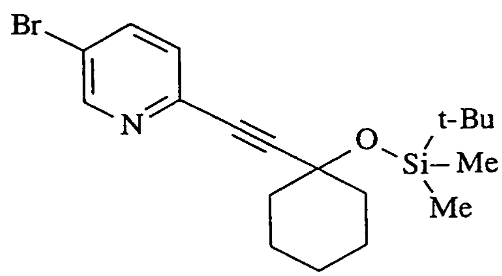
(145-1) 5-Bromo-2-[2-(1-hydroxycyclohexyl)ethynyl]pyridine




In the same manner as in Example 139-1, the title compound was obtained as a pale brown solid (14.305 g, yield; 85%) from 2,5-dibromopyridine (14.213 g) and 1-ethynylcyclopentanol (7.451 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.25-1.36(1H,m), 1.52-1.80(6H,m), 2.00-2.06(2H,m), 2.40-2.45(1H,m), 7.31(1H,d,J=8.4Hz), 7.78(11H,dd,J=8.4Hz,2.4Hz), 8.63(1H,d,J=2.4Hz).

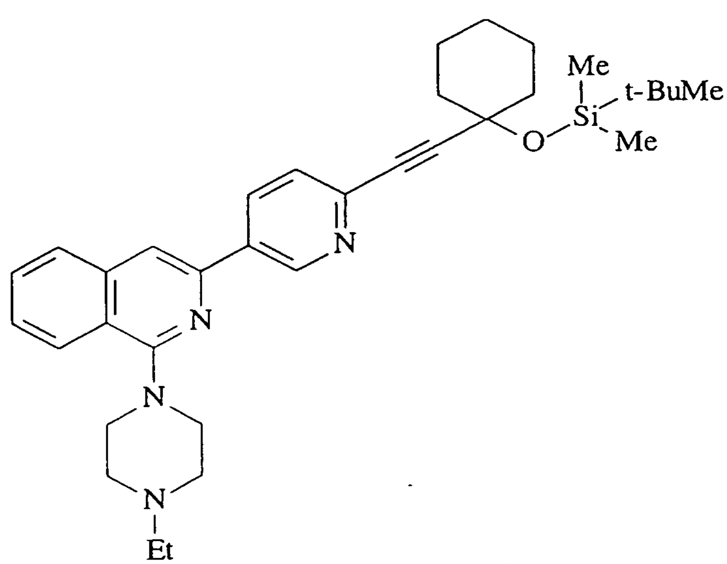
(145-2) 5-Bromo-2-[2-[1-(tert-butyldimethylsilyloxy)cyclohexyl]ethynyl]pyridine




In the same manner as in Example 138-3, the title compound was obtained as a pale yellow oil (4 g, yield; 100%) from 5-bromo-2-[2-(1-hydroxycyclohexyl)ethynyl]pyridine (2.802 g).

$^1$H-NMR(400MHz,CDCl$_3$); $\delta$ (ppm) 0.21(6H,s), 0.90(9H,s), 1.32-1.94(10H,m), 7.28(1H,d,J=8.4Hz), 7.77(1H,dd,J=8.4Hz,2.4Hz), 8.64(1H,d,J=2.4Hz).

(145-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-[2-[2-(t-butyldimethylsilyloxy)-2-cyclohexyl]ethynyl]pyridin-4-yl]isoquinoline or compound identified by the following analytical data and synthetic procedures

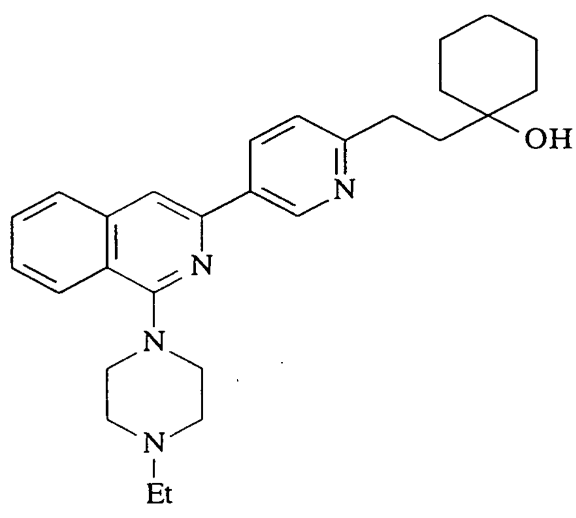



In the same manner as in Example 167-2, the title compound

was obtained as a yellow oil (156 mg, yield; 21%) from 5-bromo-2-{2-[1-(t-butyldimethylsilyloxy)cyclohexyl]ethynyl}pyridine (4 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (446 mg).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.26(6H,s), 0.92(9H,s), 1.14(3H,t,J=7.2Hz), 1.05-1.75(10H,m), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.59(4H,t,J=4.4Hz), 7.49(1H,dd,J=8.4Hz,0.8Hz), 7.50((1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.80(1H,d,J=8Hz), 8.07(1H,d,J=8Hz), 8.40(1H,dd,J=8.4Hz,2.4Hz), 9.35(1H,dd,J=2.4Hz,0.8Hz).

<u>(145-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-[2-(2-hydroxy-2-cyclohexyl)ethynyl]pyridin-4-yl]isoquinoline oxalate or compound identified by the following analytical data and synthetic procedures</u>




1-(1-Ethylpiperazin-4-yl)-3-[2-{2-[1-(t-butyldimethylsilyloxy)-2-cyclohexyl]ethynyl}pyridin-4-yl]]isoquinoline (156 mg) was dissolved in tetrahydrofuran (10

ml), followed by the addition of 1M tetrabutylammonium fluoride/tetrahydrofuran solution (0.6 ml), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was then treated in the same manner as in Example 131, to give the oxalate of the title compound as a yellow amorphous (110 mg, yield; 67%).

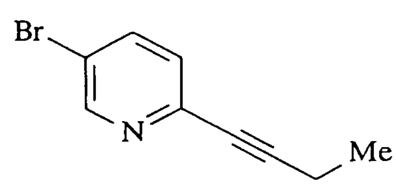
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 1.28-1.64(8H,m), 1.71-1.78(2H,m), 2.79-2.86(2H,m), 3.06(2H,q,J=7.2Hz), 3.26-3.36(4H,br-s), 3.38-3.76(4H,br-s), 7.36(1H,d,J=8Hz), 7.60(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 7,69(1H,s), 8.10(1H,dd,J=8Hz,2.4Hz), 9.24(1H,d,J=2.4Hz).

ESI-Mass; 445($MH^+$).

Example 146 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(1-butyn-1-yl)pyridin-5-yl]isoquinoline

(146-1) 5-Bromo-2-(1-butynyl)pyridine

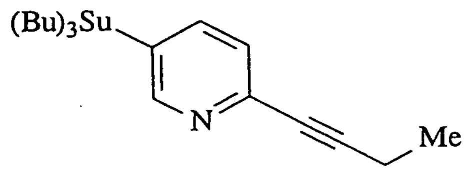



In the same manner as in Example 139-1, the title compound was obtained as a brown solid (13.113 g, yield; 60%) from 2,5-dibromopyridine (24.7 g) and 1-butyne (5.63 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.26(3H,t,J=7.6Hz),

2.44(2H,q,J=7.6Hz), 7.74(1H,dd,J=8.4Hz,2.4Hz), 8.59(1H,d,J=2.4Hz).

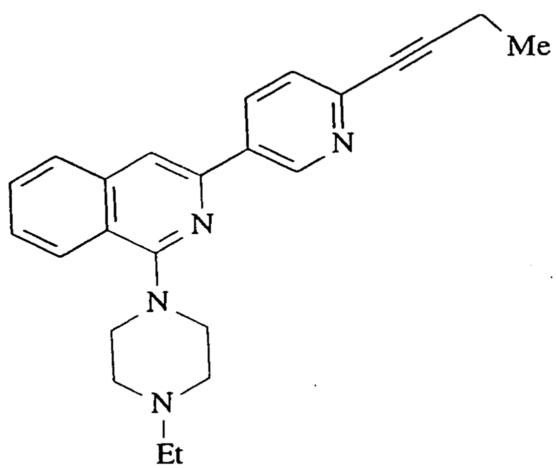
(146-2) 2-(1-Butynyl)-5-tributylstannylpyridine



In the same manner as in Example 161-2, the title compound was obtained as a pale green oil (1.331 g, yield; 25%) from 5-bromo-2-(1-butynyl)pyridine (2.521 g).

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.88(9H,t,J=7.6Hz), 1.06-1.11(6H,m), 1.26(3H,t,J=7.6Hz), 7.30(1H,dd,J=7.4Hz,1.2Hz), 7.67(1H,dd,J=7.4Hz,1.2Hz), 8.52(1H,t,J=1.2Hz).

(146-3) 1-(1-Ethylpiperazin-4-yl)-3-[2-(1-butynyl)pyridin-5-yl]isoquinoline



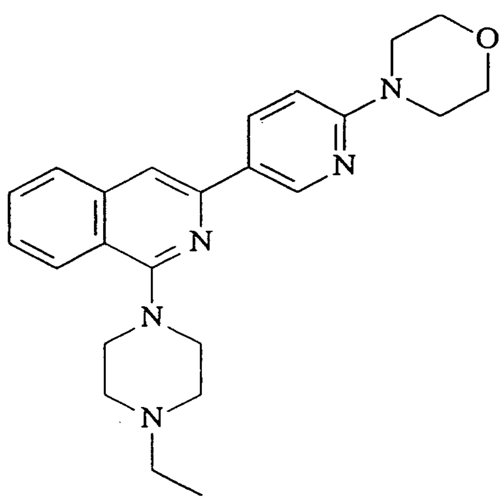
In the same manner as in Example 161-2, the title compound was obtained as a yellow amorphous (155 mg, yield; 27%) from 2-(1-butynyl)-5-tributylstannylpyridine (1.331 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (466 mg).

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 1.29(3H,t,J=7.2Hz), 2.50(2H,q,J=7.2Hz), 2.56(2H,q,J=7.2Hz), 2.75(4H,t,J=4.4Hz), 3.59(4H,t,J=4.4Hz), 7.46(1H,d,J=8Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,s), 7.82(1H,d,J=8Hz), 8.09(1H,d,J=8Hz), 8.40(1H,dd,J=8Hz,2.4Hz), 9.29(1H,d,J=2.4Hz).

ESI-Mass; 371($MH^+$).

Example 147 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(morpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.27 g) and [2-(morpholin-4-yl)pyridin-5-yl]tributylstannum (3.03 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, and then it was partitioned. The resulting organic layer was washed with water and brine, and

then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.39 g of the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.54(m,4H), 3.59(br-t,4H), 3.85(m,4H), 6.72(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.55(s,1H), 7.56(br-t,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.27(dd,J=8.4,2.4Hz,1H), 9.02(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.51 g of the title compound as a white powder.

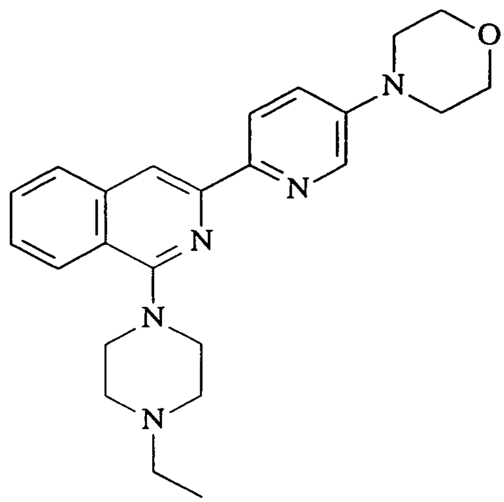
Hydrochloride:

m.p.; 186°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.23(m,2H), 3.36(m,2H), 3.51(br-t,2H), 3.63(br-d,2H), 3.68(m,4H), 3.77(m,4H), 4.00(br-d,2H), 7.26(m,1H), 7.61(br-t,1H), 7.75(br-t,1H), 7.95(br-d,1H), 8.08(s,1H), 8.11(br-d,1H), 8.54(m,1H), 8.86(br-s,1H).

MS(FAB) m/z 404(M+H)$^+$.

Example 148 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[5-(morpholin-4-yl)pyridin-2-yl]isoquinoline trihydrochloride



3-(5-Bromopyridin-2-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline (0.21 g) and morpholine (0.12 ml) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, and partitioned. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 47 mg of the free compound of the title compound as a colorless oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.20(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.79(br-s,4H), 3.27(m,4H), 3.59(br-s,4H), 3.91(m,4H), 7.30(dd,J=8.8,2.8Hz,1H), 7.46(br-t,1H), 7.58(br-t,1H), 7.85(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H), 8.26(s,1H), 8.37(d,J=2.8Hz,1H), 8.41(d,J=8.8Hz,1H).

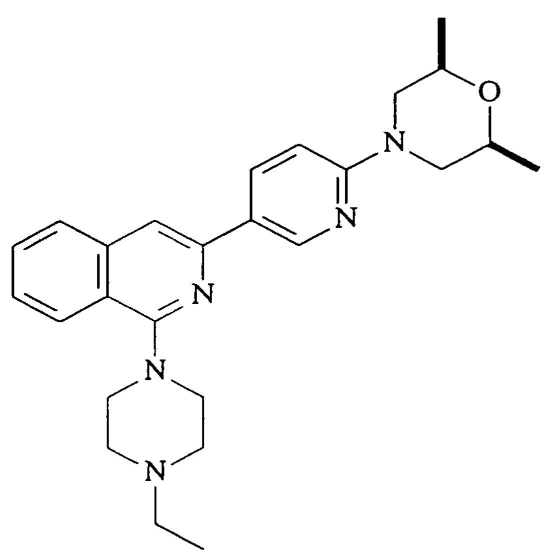
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 52 mg of the free compound of the title compound as a white powder.

Hydrochloride:

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.24(m,2H), 3.32-3.42(m,6H), 3.50-3.65(m,4H), 3.81(m,4H), 4.13(br-d,2H), 7.69(br-t,1H), 7.81(br-t,1H), 7.94(br,1H), 8.04(br-d,1H), 8.16(br-d,1H), 8.36(br-d,1H), 8.45(br-s,1H), 8.48(br-d,1H).

MS (FAB) m/z 404(M+H)$^+$.

Example 149 Synthesis of 3-[2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (2.00 g) and [2-(2,6-dimethylmorpholin-4-yl)pyridin-5-yl]tributylstannum (5.70 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (70

ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.76 g of the free compound of the title compound as a colorless oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.30(d,J=6.0Hz,6H), 2.57(q,J=7.2Hz,2H), 2.60(dd,J=13.0,10.4Hz,6H), 2.76(br-t,4H), 3.60(br-t,4H), 3.76(ddd,J=10.4,6.0,2.0Hz,2H), 4.14(dd,J=13.0,2.0,2H), 6.72(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.55(s,1H), 7.57(br-t,1H), 7.76(d,J=8.0,1H), 8.04(d,J=8.0,1.0Hz,1H), 8.26(dd,J=8.0,2.4Hz,1H), 9.02(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 1.08 g of the hydrochloride of the title compound as a white powder.

Hydrochloride:

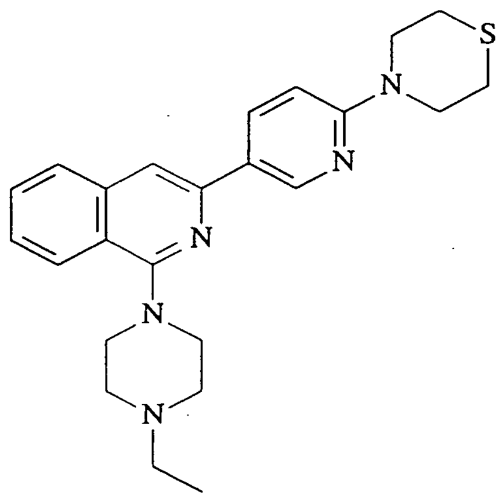
m.p.; 180°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.19(d,J=5.6Hz,6H), 1.32(t,J=7.2Hz,3H), 2.62-2.68(m,2H), 3.24(m,2H), 3.37(m,2H), 3.48(br-t,2H), 3.60-3.70(m,4H), 4.01(br-d,2H), 4.29(br-d,2H),

7.24(m,1H), 7.60(br-t,1H), 7.55(br-t,1H), 7.75(br-t,1H), 7.95(br-d,1H), 8.05(br-s,1H), 8.11(br-d,1H), 8.49(m,1H), 8.86(br-s,1H).

MS(FAB) m/z 432(M+H)$^+$.

Example 150 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.69 g) and [2-(thiomorpholin-4-yl)pyridin-5-yl]tributylstannum (1.62 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.50 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated. Ethyl acetate and an aqueous solution of saturated sodium bicarbonate were added to the resulting residue, for partitioning. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene

chloride/methanol system), to give 0.66 g of the free compound of the title compound as a white amorphous.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.24(br-s,3H), 2.64(br-s,2H), 2.70(m,4H), 2.80(br,4H), 3.67(br,4H), 4.04(m,4H), 6.42(d,J=8.8Hz,2H), 7.43(br-t,1H), 7.56(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H), 8.24(dd,J=8.8,2.4Hz,1H), 9.00(d,J=2.4Hz,1H).

The resulting free compound (0.20 g) was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.26 g of the hydrochloride of the title compound as a pale yellow powder.

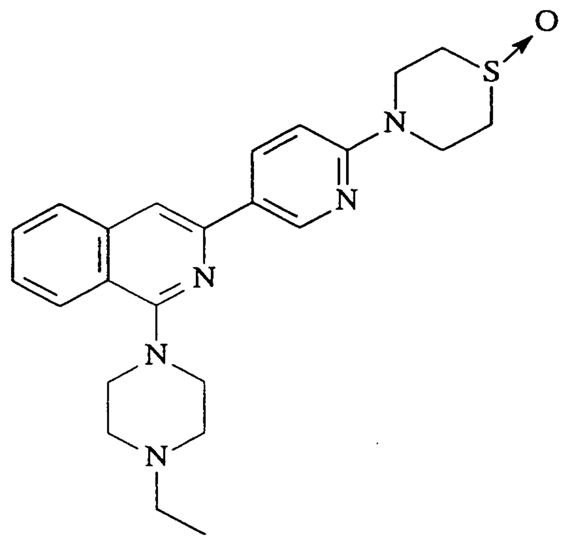
Hydrochloride:

m.p.; 210°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 2.75(br-s,4H), 3.20-3.27(m,2H), 3.47-3.56(m,2H), 3.60-3.66(br-d,2H), 3.97-4.02(br-d,2H), 4.10(br-s,4H), 7.37(m,1H), 7.62(br-t,1H), 7.77(br-t,1H), 7.96(br-d,1H), 8.09-8.14(m,1H), 8.58(m,1H), 8.80(m,1H), 10.9(m,1H).

MS(FAB) m/z 420(M+H)$^+$.

Example 151 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(S-oxythiomorpholin-4-yl)pyridin-5-yl]isoquinoline trihydrochloride



1-(4-Ethylpiperazin-1-yl)-3-[2-(thiomorpholin-4-yl)pyridin-5-yl]isoquinoline (0.10 g) obtained in Example 150 was dissolved in dichloromethane (10 ml), and the resulting solution was reacted with 3-chloroperbenzoic acid (56 mg) under ice-cooling for 1 hr. The reaction solution was partitioned between ethyl acetate and an aqueous solution of saturated sodium bicarbonate. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 28 mg of the free compound of the title compound as a colorless oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.22(t,J=7.2Hz,3H), 2.63(q,J=7.2Hz,2H), 2.79-2.88(m,8H), 3.65(br-s,4H), 4.22(m,4H), 6.82(d,J=8.8Hz,2H), 7.45(br-t,1H), 7.58(br-t,1H), 7.76(d,J=8.0Hz,1H), 8.03(d,J=8.0Hz,1H),

8.28(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

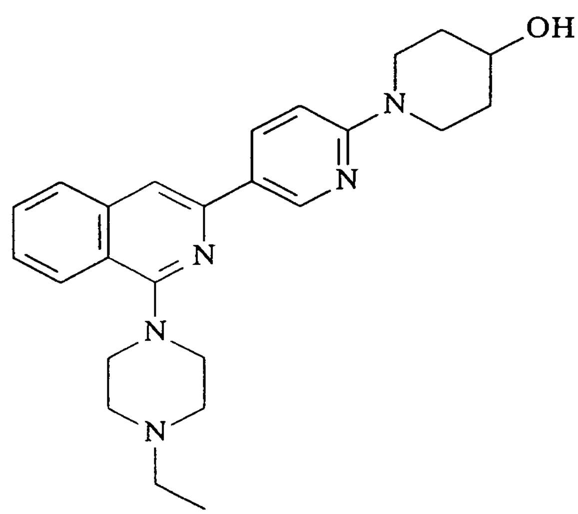
The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 40 mg of the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

m.p.; 170°C

MS(FAB) m/z 436(M+H)$^+$.

Example 152 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxypiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride




3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.16 g) and {2-[4-(t-butyldimethyloxy)piperidin-1-yl]pyridin-5-yl}tributylstannum (1.37 g) was reacted in the presence of tetrakistriphenylphosphine dichloride (0.30 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated. A 2N aqueous solution of hydrochloric acid was added to the resulting residue, and then reacted at 50°C for 1 hr. The

reaction solution was basified with a 2N aqueous solution of sodium hydroxide, and then it was extracted with ethyl acetate. The resulting organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.26 g of the free compound of the title compound as a colorless amorphous.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.33(dd,J=12.0,4.0Hz,2H), 1.43(dt,J=0.8,6.0Hz,1H), 1.86(br-d,J=12Hz,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 2.92(dt,2.4,12.8Hz,2H), 3.55(t,J=6Hz,2H), 3.59(br-s,4H), 4.44(br-d,J=12.8,2H), 6.76(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.30 g of the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

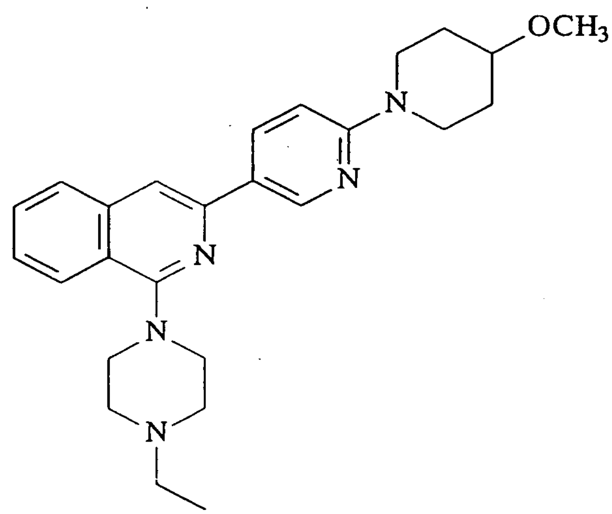
m.p.; 188°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.27(br-d,J=13.4Hz,3H), 1.34(t,J=7.2Hz,3H), 1.73-1.86(m,1H), 1.83(br-d,J=13.4,2H), 3.23(m,2H), 3.31(m,2H), 3.32-3.37(m,2H), 3.42-3.56(m,4H), 3.98(br-d,2H), 4.41(br-d,2H), 7.52(br-d,1H), 7.64(br-

t,J=7.6Hz,1H), 7.78(br-t,J=7.6Hz,1H), 7.97(br-d,J=7.6Hz,1H), 8.11-8.15(m,1H), 8.13(s,1H), 8.65(br-d,J=7.6Hz,1H), 8.68(br-s,1H), 11.14(br-s,1H).

MS(FAB) m/z 432(M+H)$^+$.

Example 153 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-methoxypiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (0.83 g) and [2-(4-methoxypiperidin-1-yl)pyridin-5-yl]tributylstannum (0.94 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.40 g) in xylene (30 ml) at 140°C for 5 hr. The reaction solution was concentrated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system), to give 0.61 g of the free compound of the title compound as a pale yellow

oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.65(m,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 3.31(ddd,J=13.2,9.6,3.6Hz,2H), 3.40(s,3H), 3.59(br-s,4H), 4.06(m,2H), 6.77(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.76(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.62 g of the hydrochloride of the title compound as a white powder.

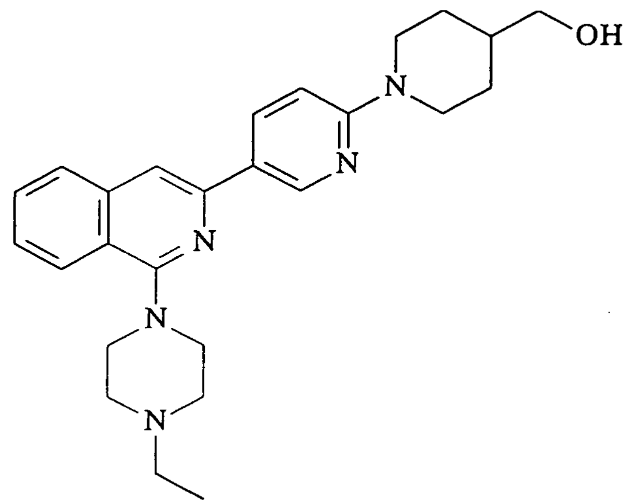
Hydrochloride:

m.p.; 170°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.35(t,J=7.2Hz,3H), 1.58-1.68(m,2H), 1.95-2.04(m,2H), 3.23(m,2H), 3.31(s,3H), 3.38(m,2H), 3.51-3.59(m,5H), 3.64(m,2H), 3.97(br-d,2H), 4.02(m,2H), 7.54(br-d,1H), 7.64(br-t,1H), 7.78(br-t,1H), 7.97(br-d,1H), 8.11-8.15(m,2H), 8.65-8.70(m,2H), 11.34(br-s,1H).

MS(FAB) m/z 432$(M+H)^+$.

Example 154 Synthesis of 1-(4-ethylpiperazin-1-yl)-3-[2-(4-hydroxymethylpiperidin-1-yl)pyridin-5-yl]isoquinoline trihydrochloride



3-Bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (1.35 g) and [2-(4-ethoxycarbonylpiperidin-1-yl)pyridin-5-yl]tributylstannum (1.71 g) were reacted in the presence of tetrakistriphenylphosphine dichloride (0.40 g) in xylene (50 ml) at 140°C for 5 hr. The reaction solution was concentrated and partitioned between ethyl acetate and water. The resulting organic layer was washed with water and brine, and then dried over magnesium sulfate. The solvent was evaporated. The resulting residue in a pale yellow oil was dissolved in tetrahydrofuran (30 ml) and reacted with lithium aluminium hydride (1.9 ml, 1M-THF solution). Water (0.07 ml), a 5N aqueous solution of sodium hydroxide (0.07 ml) and water (0.21 ml) were added to the reaction solution in this order, which was stirred at room temperature for 1 hr. The reaction solution was filtered, and the resulting insoluble matters were washed with ethyl acetate, while the resulting filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system),

to give 0.78 g of the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 1.33(dd,J=12.0,4.0Hz,2H), 1.43(dt,J=0.8,6.0Hz,1H), 1.86(br-d,J=12,2H), 2.56(q,J=7.2Hz,2H), 2.76(br-s,4H), 2.92(dt,2.4,12.8Hz,2H), 3.55(t,J=6Hz,2H), 3.59(br-s,4H), 4.44(br-d,J=12.8,2H), 6.76(d,J=8.8Hz,1H), 7.42(br-t,1H), 7.54(s,1H), 7.75(d,J=8.0Hz,1H), 8.04(d,J=8.0Hz,1H), 8.23(dd,J=8.8,2.4Hz,1H), 9.01(d,J=2.4Hz,1H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give 0.45 g of the hydrochloride of the title compound as a white powder.

Hydrochloride:

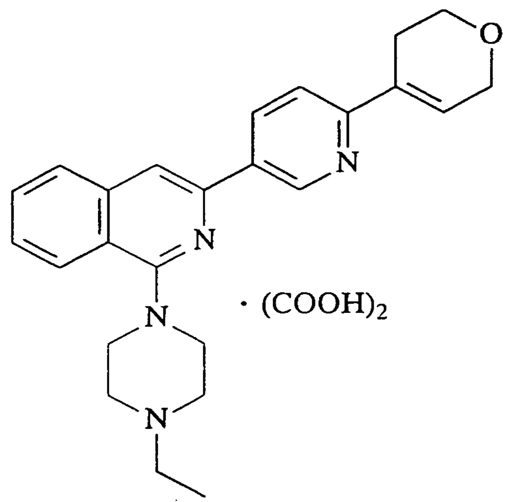
m.p.; 188°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.27(br-d,J=13.4Hz,3H), 1.34(t,J=7.2Hz,3H), 1.73-1.86(m,1H), 1.83(br-d,J=13.4,2H), 3.23(m,2H), 3.31(m,2H), 3.32-3.37(m,2H), 3.42-3.56(m,4H), 3.98(br-d,2H), 4.41(br-d,2H), 7.52(br-d,1H), 7.64(br-t,J=7.6Hz,1H), 7.78(br-t,J=7.6Hz,1H), 7.97(br-d,J=7.6Hz,1H), 8.11-8.15(m,1H), 8.13(s,1H), 8.65(br-d,J=7.6Hz,1H), 8.68(br-s,1H), 11.14(br-s,1H).

MS(FAB) m/z 432$(M+H)^+$.

Example 155 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline

oxalate



In the same manners sequentially as in Examples 161-2 and 20, a yellow oil was obtained (127 mg, yield; 90%) from 5-bromo-2-(5,6-dihydro-2H-pyran-4-yl)pyridine (432 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (111 mg). The resulting compound was converted into a oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 156-159°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(br,3H), 2.51(br,2H), 3.06(br,2H), 3.32(br,4H), 3.67(br,4H), 3.84(br,2H), 4.26(br,2H), 6.47(s,1H), 7.63(br,1H), 7.96(d,J=8.0Hz,1H), 8.06-8.13(m,2H), 8.38(d,J=8.0Hz,1H), 8.45(s,1H), 8.78(s,1H).

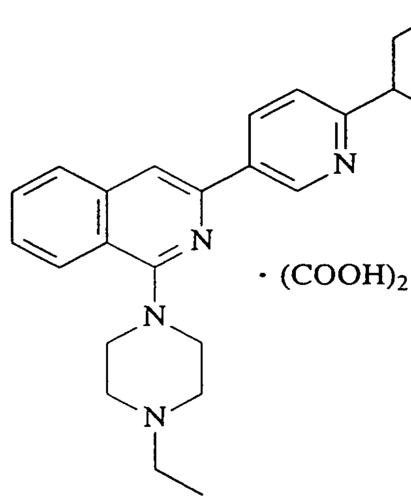
MS(FAB) m/z 401(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.16(t,J=7.2Hz,3H), 2.54(q,J=7.2Hz,2H), 2.88(t,J=8.0Hz,1H), 2.73(br,4H),

3.52(br,4H), 3.99(t,J=5.6Hz,2H), 4.38(q,J=2.8Hz,2H), 6.28(br,1H), 7.49(t,J=8.0Hz,1H), 7.61(t,J=8.0Hz,1H), 7.80(dd,J=8.4,2.4Hz,1H), 7.89(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H), 8.38(s,1H), 8.49(d,J=8.4Hz,1H), 8.74(d,J=2.4Hz,1H).

Example 156 Synthesis of 3-[2-(tetrahydropyran-4-yl)pyridin-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate



In the same manners sequentially as in Examples 161-2 and 20, an oil was obtained from 5-bromo-2-(tetrahydropyran-4-yl)pyridine (745 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). Methanol (10 ml) and palladium-carbon catalyst (25 mg) were added to the oil (387 mg), and then reacted in hydrogen atmosphere overnight. The resulting reaction solution was filtered through Celite, and then evaporated. The resulting residue was basified by adding a 1N aqueous solution of sodium hydroxide thereto, and then it was partitioned between ethyl acetate and water. The resulting

organic layer was washe with water, dried and concentrated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system), to give a yellow oil (260 mg, yield; 69%). The resulting oil was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as white crystals.

Oxalate:

m.p.; 158-160°C

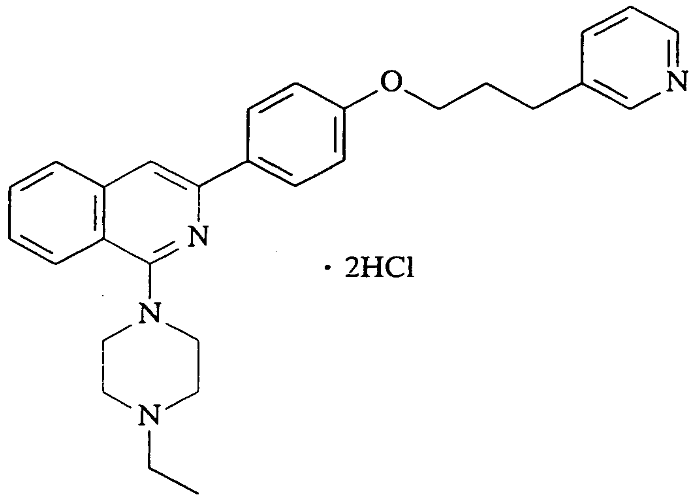
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.27(t,J=7.2Hz,3H), 1.76(br,4H), 2.92(br,1H), 3.19(br,2H), 3.30-3.85(m,10H), 3.99(d,J=11.2Hz,2H), 7.65(t,J=8.0Hz,1H), 7.76(t,J=8.0Hz,1H), 7.86(dd,J=8.4,2.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.14(d,J=8.4Hz,1H), 8.37(d,J=8.0Hz,1H), 8.46(s,1H), 8.61(d,J=2.0Hz,1H).

MS(FAB) m/z 403(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=6.8Hz,3H), 1.82-1.92(m,4H), 2.57(q,J=6.8Hz,2H), 2.78(br,4H), 2.78-2.98(m,1H), 3.55-3.59(m,6H), 4.11-4.14(m,2H), 7.50(t,J=8.4Hz,1H), 7.61(t,J=8.4Hz,1H), 7.68(dd,J=8.4,2.4Hz,1H), 7.89(d,J=8.4Hz,1H), 8.11(d,J=8.4Hz,1H), 8.36(s,1H), 8.48(d,J=8.4Hz,1H), 8.57(d,J=2.4Hz,1H).

Example 157 Synthesis of 3-[4-[3-(3-pyridyl)propoxy]phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 51, the free compound of the title compound was obtained (62 mg, yield; 23%) from 3-(4-hydroxyphenyl)-1-(4-ethylpiperazin-1-yl)isoquinoline (201 mg) and 3-(3-methanesulfonate propyl)pyridine (194 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

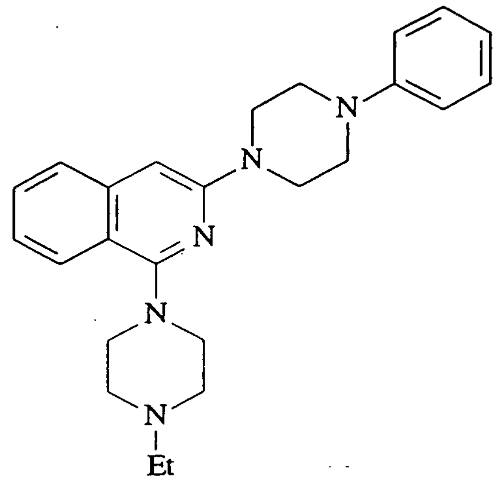
Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.10-2.18(m,2H), 2.57(q,J=7.2Hz,2H), 2.78(br,4H), 2.85(t,J=7.6Hz,2H), 3.60(br,4H), 4.04(t,J=6.0Hz,2H), 6.98(d,J=8.8Hz,2H), 7.22(dd,J=7.6,4.4Hz,1H), 7.43(dt,J=8.0,1.2Hz,1H), 7.53-7.56(m,1H), 7.56(dt,J=8.0,1.2Hz,1H), 7.62(s,1H), 7.76(d,J=8.0Hz,1H), 8.05(d,J=8.0Hz,1H), 8.11(d,J=8.8Hz,2H), 8.46(dd,J=4.4,1.6Hz,1H), 8.51(d,J=2.0Hz,1H).

MS(FAB) m/z 453$(M+H)^+$.

Example 158 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(1-

phenylpiperazin-4-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (631 mg) was dissolved in dioxane (15 ml), followed by the addition of 1-phenylpiperazine (331 mg), tris(dibenzylideneacetone)(chloroform)dipalladium (0) (10 mg), tri-o-tolylphosphine (12 mg) and t-butoxysodium (231 mg), and the resulting mixture was stirred in nitrogen atmosphere at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a gray amorphous (196 mg, yield; 20%).

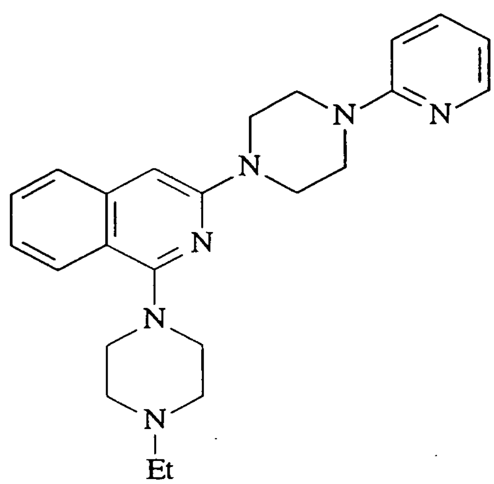
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(3H,t,J=7.2Hz), 3.08(2H,q,J=7.2Hz), 3.24-3.32(8H,m), 3.46-3.62(4H,m), 3.63(4H,t,J=4.4Hz), 6.67(1H.s), 6.80(2H,d,J=8.8Hz),

7.21(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.23(1H,dd,J=8.8Hz,7.2Hz), 7.49(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.63(1H,d,J=8Hz), 7.87(1H,d,J=8Hz).

ESI-Mass; 402($MH^+$).

Example 159 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[1-(2-pyridyl)piperazin-4-yl]isoquinoline



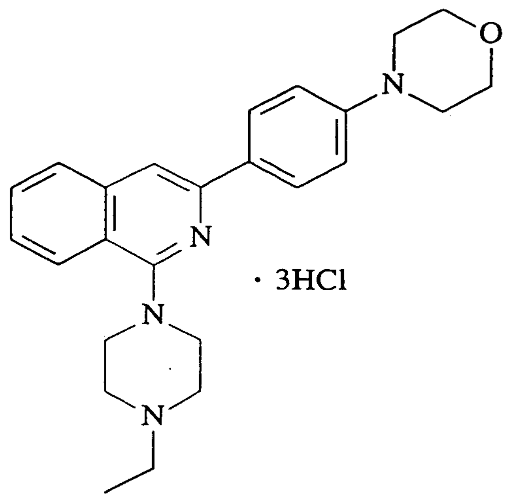
In the same manner as in Example 158, the oxalate of the title compound was obtained as a pale amorphous (533 mg, yield; 42%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (760 mg) and 1-(2-pyridyl)piperazine (1.162 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 3.10(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.64(4H,m), 3.57-3.66(8H,m), 6.65(1H,ddd,J=7Hz,5Hz,0.8Hz), 6.66(1H,s), 6.89(1H,d,J=8.8Hz), 7.21(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.48(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8.8Hz,7Hz,2Hz), 7.62(1H,d,J=8Hz), 7.87(1H,d,J=8Hz), 8.13(1H,ddd,J=5Hz,2Hz,0.8Hz).

ESI-Mass ; 403($MH^+$).

Example 160 Synthesis of 3-[4-(4-morpholinyl)phenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline dihydrochloride



4-(4-Morpholinyl)benzonitrile obtained by reacting 4-fluorobenzonitrile (10.89 g) and morpholine (7.84 g) in the presence of potassium carbonate (12.42 g) in dimethyl sulfoxide (45 ml) was reacted with N-methyl-o-toluamide (8.019 g) according to Example 10-1, to give 6.840 g of 3-[4-(4-morpholinyl)phenyl]isoquinolin-1-one.

The resulting 3-[4-(4-morpholinyl)phenyl]isoquinolin-1-one (1.523 g) was reacted in the same manner as in Example 66, and then purified by silica gel column chromatography (chloroform/methanol system), to give 1.623 g of the free compound of the title compound as a pale yellow oil.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.75(br-t,4H), 3.23(t,J=4.8Hz,4H), 3.58(br-t,4H), 3.88(t,J=4.8Hz,4H), 6.99(d,J=9.0Hz,2H),

7.41(br-t,1H), 7.55(br-t,1H), 7.60(s,1H), 7.75(d,J=8.0Hz,1H), 8.05(d,J=8.4Hz,1H), 8.11(d,J=9.0Hz,2H).

The resulting free compound was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/ether, to give the hydrochloride of the title compound as a yellow powder.

Hydrochloride:

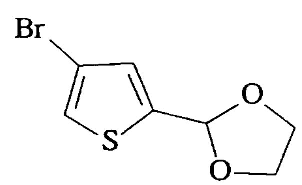
m.p.; 242-245°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.19-3.28(m,6H), 3.30-3.38(m,2H), 3.54(br-t,2H), 3.62(br-d,2H), 3.82(br-t,4H), 3.98(br-d,2H), 7.19(d,J=8.6Hz,2H), 7.56(br-t,1H), 7.71(br-t,1H), 7.95(d,J=7.6Hz,1H), 7.98(s,1H), 8.09(d,J=8.4Hz,1H), 8.12(d,J=8.6Hz,2H), 11.13(br-s,1H).

MS(FAB) m/z 403(M+H)$^+$.

Example 161 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline dihydrochloride

(161-1) 2-(4-Bromothiophen-2-yl)-1,3-dioxolane

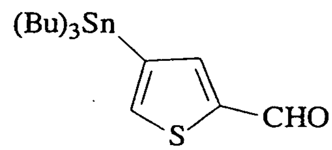



4-Bromo-2-thiophenecarboxyaldehyde (50 g) was dissolved in toluene (500 ml), followed by the addition of ethylene glycol (81 g) and p-toluenesulfonic acid (572 mg). The resulting mixture was heated under reflux overnight with a Dean-Stark apparatus. After cooling as it was, the reaction mixture was washed sequentially with an aqueous solution of saturated

sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (55 g, yield; 89%).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 4.00-4.13(4H,m), 6.06(1H,s), 7.08(1H,d,J=1.2Hz), 7.21(1H,d,J=1.2Hz).

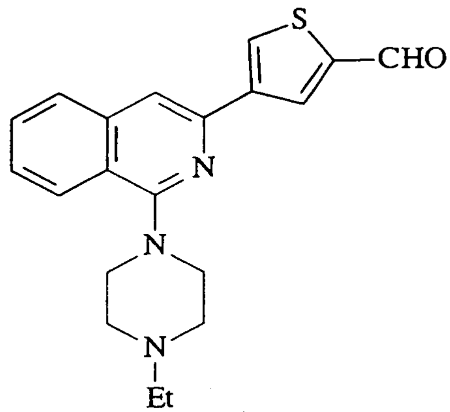
(161-2) 4-Tributylstannyl-2-thiophenecarboxyaldehyde



2-(4-Bromothiophen-2-yl)-1,3-dioxolane (2.351 g) was dissolved in xylene (30 ml), followed by the addition of bis(tributyltin) (5.1 ml) and tetrakis(triphenylphosphine) palladium (116 mg). The resulting mixture was heated under stirring in nitrogen atmosphere at 120°C for 1 hr. After the resulting insoluble matters were filtered off, the resulting solution was evaporated, and then purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (1.165 g, yield; 29%).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 0.90(9H,t,J=7.2Hz), 1.07-1.12(6H,m), 1.28-1.38(6H,m), 1.50-1.58(6H,m), 7.72(1H,d,J=1.2Hz), 7.79(1H,d,J=1.2Hz), 7.79(1H,d,J=1.2Hz), 9.99(1H,d,J=1.2Hz).

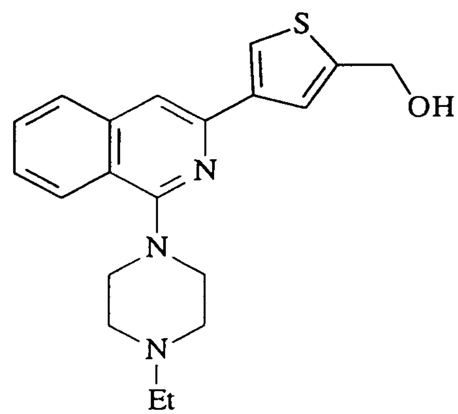
(161-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (356 mg) was dissolved in xylene (30 ml), followed by the addition of 4-tributylstannyl-2-thiophenecarboxyaldehyde (1.165 g) and tetrakis(triphenylphosphine)palladium (35 mg). The resulting mixture was heated under stirring in nitrogen atmosphere at 120°C overnight. Then, it was diluted with ethyl acetate and extracted with 2N hydrochloric acid. The resulting aqueous layer was washed with ethyl acetate, basified with 8N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting product was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (265 mg, yield; 73%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 2.56(2H,q,J=7.2Hz), 2.76(4H,t,J=4.4Hz), 3.57(4H,t,J=4.4Hz), 7.48(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55((H,ddd,J=8Hz,7Hz,1.2Hz), 7.77(1H,d,J=8Hz), 8.07(1H,d,J=8Hz), 8.37(2H,s), 10.00(1H,s).

<u>(161-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-4-yl)isoquinoline dihydrochloride</u>



1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline (141 mg) was dissolved in ethanol (10 ml), followed by the addition of sodium borohydride (8 mg) under ice-cooling, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (130 mg, yield; 75%).

Hydrochloride:

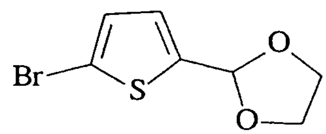
m.p.; 170°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 3.15-3.22(2H,m), 3.29(1H,t,J=11Hz), 3.32(1H,t,J=11Hz), 3.49(2H,t,J=13.4Hz), 3.57(2H,d,J=11Hz), 3.94(2H,d,J=13.4Hz), 4.66(2H,s), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,d,J=1.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,s), 7.89(1H,d,J=8Hz), 8.02(1H,d,J=1.6Hz), 8.05(1H,d,J=8Hz).

ESI-Mass ; 354 $(MH^{+})$.

Example 162 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline dihydrochloride

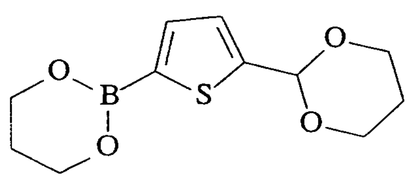
(162-1) 2-(5-Bromothiophen-2-yl)-1,3-dioxolane



In the same manner as in Example 161-1, the title compound was obtained as a brown oil (57.2 g, yield; 93%) from 5-bromo-2-thiophenecarboxaldehyde (50 g).

$^{1}$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 3.96-4.13(4H,m), 6.01(1H,s), 6.90(1H,d,J=3.6Hz), 6.93(1H,d,J=3.6Hz).

(162-2) [5-(1,3-Dioxan-2-yl)thiophen-2-yl]-1,3,2-dioxaborylate

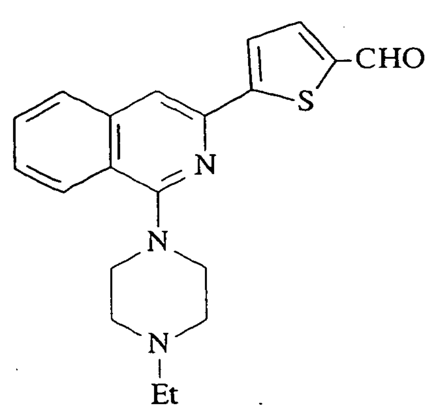


2-(5-Bromothiophen-2-yl)-1,3-dioxolane (2.351 g) was dissolved in tetrahydrofuran (10 ml), to which was then added 2.5 M n-butyl lithium/hexane solution (4 ml) in nitrogen atmosphere at -78 °C, and the mixture was stirred for 30 min. Then, trimethoxyborane (1.3 ml) was added thereto, and the mixture was stirred for 30 min, and then it was stirred at room temperature for 30 min. 2N Hydrochloric acid (10 ml) was added to the reaction mixture, and then the mixture was stirred for 30 min. Thereafter, the resulting mixture was extracted with

ether. The resulting organic layer was evaporated. The resulting residue was dissolved in ether, followed by the addition of trimethylene glycol (529 mg). The resulting mixture was stirred at room temperature for 90 min, and then evaporated. The resulting residue was dissolved in toluene, followed by the addition of trimethylene glycol (3.517 g) and p-toluenesulfonic acid (9 mg), and the resulting mixture was heated under reflux with a Dean-Stark apparatus for 3 hr. After cooling as it was, the reaction mixture was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a pale yellow oil (1.516 g, yield; 60%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.40-1.46(1H,m), 2.00-2.08(2H,m), 2.15-2.28(1H,m), 3.93-4.00(2H,m), 4.13(4H,t,J=5Hz), 4.20-4.28(2H,m), 5.74(1H,s), 7.15(1H,d,J=3.6Hz), 7.40(1H,d,J=3.6Hz).

(162-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline

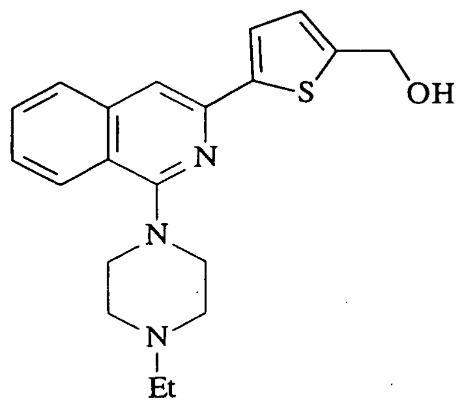



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (480 mg) was dissolved in N,N-dimethylformamide (12 ml), followed by the

addition of [5-(1,3-dioxan-2-yl)thiophen-2-yl]-1,3,2-dioxaborate (643 mg), tetrakis(triphenylphosphine)palladium (23 mg) and cesium carbonate (977 mg), and the resulting mixture was heated under stirring in nitrogen atmosphere at 100°C overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting product was purified by silica gel column chromatography (toluene/acetone system), and then dissolved in tetrahydrofuran (10 ml). 1N Hydrochloric acid (10 ml) was added thereto, and the mixture was stirred for 1 hr. The reaction solution was basified by adding 5N sodium hydroxide thereto, followed by the extraction with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a brown solid (494 mg, yield; 93%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(3H,t,J=7.2Hz), 2.54(2H,q,J=7.2Hz), 2.73(4H,t,J=4.8Hz), 3.62(4H,t,J=4.8Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.66(1H,s), 7.70(1H,d,J=4Hz), 7.77(1H,d,J=4Hz), 7.79(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 9.92(1H,s).

(162-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiophen-5-yl)isoquinoline dihydrochloride



In the same manner as in Example 161-4, the hydrochloride of the title compound was obtained as a yellow crystals (130 mg, yield; 75%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiophen-5-yl)isoquinoline (120 mg).

Hydrochloride:

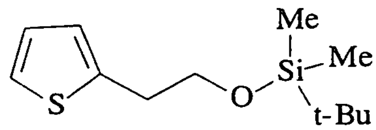
m.p.; 180 °C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.29(3H,t,J=7.2Hz), 3.15-3.25(2H,m), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.45(2H,t,J=13.4Hz), 3.59(2H,d,J=11.2Hz), 3.93(2H,d,J=13.4Hz), 4.63(2H,s), 6.97(1H,d,J=3.6Hz), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.61(1H,d,J=3.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(1H,s), 7.89(1H,d,J=8Hz), 8.05(1H,d,J=8Hz).

ESI-Mass; 354($MH^+$).

<u>Example 163 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline dihydrochloride</u>

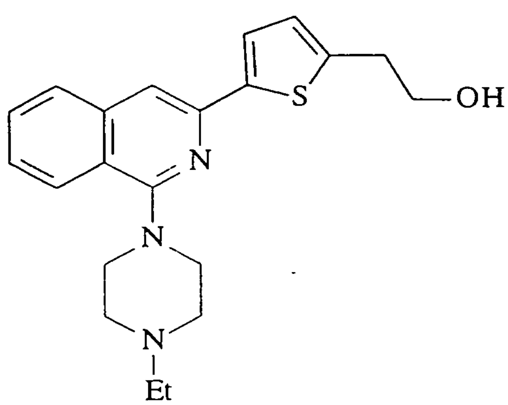
<u>(163-1) 2-[2-(t-Butyldimethylsilyloxy)ethyl]thiophene</u>



2-(2-Thienyl)ethanol (2.6 g) was dissolved in N,N-dimethylformamide (20 ml), followed by the addition of t-butyldimethylsilyl chloride (3.667 g) and imidazole (1.634 g), and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless oil (4.87 g, yield; 100%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 0.03(6H,s), 0.89(9H,s), 3.04(2H,t,J=6.8Hz), 3.82(2H,t,J=6.8Hz), 6.83(1H,dd,J=3.6Hz,1Hz), 6.93(1H,dd,J=5Hz,3.6Hz), 7.13(1H,dd,J=5Hz,1Hz).

(163-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethyl)thiophen-5-yl]isoquinoline dihydrochloride



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as yellow brown crystals (722 mg, yield; 64%) from 2-[2-(t-butyldimetylsilyloxy)ethyl]thiophene (2.435 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (809 mg).

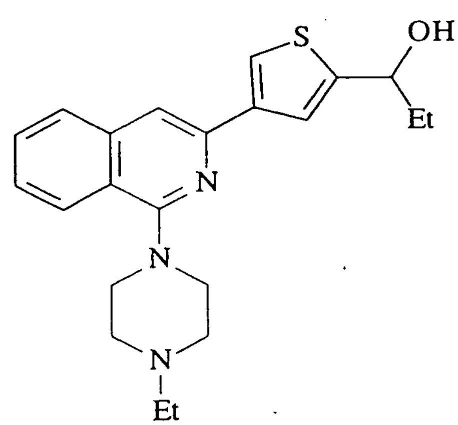
Hydrochloride:

m.p.; 129-134°C

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.30(3H,t,J=7.2Hz), 2.93(2H,t,J=6.4Hz), 3.15-3.24(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.45(2H,t,J=13.2Hz), 3.59(2H,d,J=11.6Hz), 3.63(2H,t,J=6.4Hz), 3.91(2H,d,J=13.2Hz), 6.90(1H,d,J=3.6Hz), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.58(1H,d,J=3.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.85(1H,s), 7.88(1H,d,J=8Hz), 8.04(1H,d,J=8Hz), 10.75(1H,br-s).

ESI-Mass; 368($MH^+$).

Example 164 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-4-yl]isoquinoline hydrochloride




In the same manner as in Example 260, the hydrochloride of the title compound was obtained as a brown amorphous (226

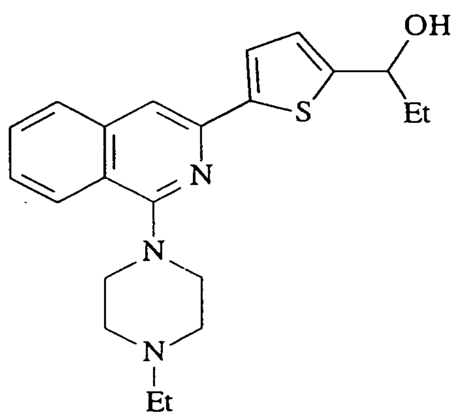
mg, yield; 73%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiophen-4-yl)isoquinoline (233 mg) and 3M ethylmagnesium bromide (0.7 ml).

Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.89(3H,t,J=7.4Hz), 1.22(3H,t,J=7.2Hz), 1.70-1.78(2H,m), 2.97-3.07(2H,br-s), 3.18-3.32(4H,br-s), 3.47-3.72(4H,br-s), 4.72(1H,t,J=6.4Hz), 7.54(1H,dd,J=8Hz,7Hz), 7.58(1H,s), 7.69(1H,dd,J=8Hz,7Hz), 7.84(1H,s), 7.88(1H,d,J=8Hz), 7.98(1H,s), 8.05(1H,d,J=8Hz).

ESI-Mass; 382(MH$^+$).

Example 165 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[2-(1-hydroxypropyl)thiophen-5-yl]isoquinoline hydrochloride




In the same manner as in Example 260, the hydrochloride of the title compound was obtained as a brown amorphous (197 mg, yield; 79%) from 1-(1-ethylpiperazin-4-yl)-3-(2-fomylthiophen-5-yl)isoquinoline (181 mg) and 3M ethylmagnesium bromide (0.7 ml).

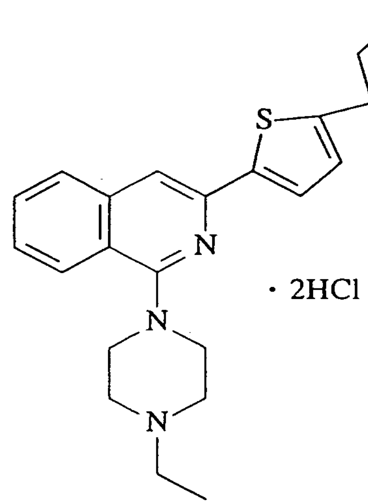
Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.88(3H,t,J=7.4Hz),

1.19(3H,t,J=7.2Hz), 1.68-1.74(2H,m), 2.90-3.02(2H,br-s), 3.10-3.27(4H,br-s), 3.45-3.62(4H,br-s), 4.68(1H,t,J=6.4Hz), 6.94(1H,d,J=3.6Hz), 7.52(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.59(1H,d,J=3.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.84(1H,s), 7.87(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 382($MH^+$).

Example 166 Synthesis of 3-[2-(tetrahydropyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (330 mg, yield; 86%) from 4-bromo-2-(tetrahydropyran-4-yl)thiophene (700 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 251-253°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 1.62-1.74(m,2H), 1.94(br,1H), 3.06-3.16(m,2H), 3.18-3.26(m,2H), 3.30-3.38(m,2H), 3.42-3.52(m,4H), 3.61(d,J=11.6Hz,2H), 3.94(d,J=14.0Hz,4H), 6.96(d,J=4.0Hz,1H), 7.56(t,J=8.0Hz,1H), 7.64(t,J=4.0Hz,1H), 7.72(d,J=8.0Hz,1H), 7.89(s,1H), 7.91(d,J=8.0Hz,1H), 8.07(d,J=8.0Hz,1H).

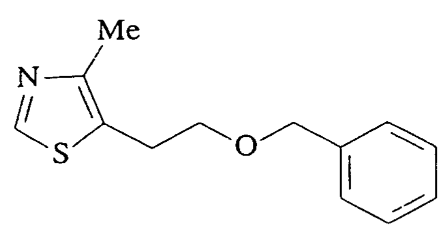
MS(FAB) m/z 408$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 1.83-2.05(m,4H), 2.55(q,J=7.2Hz,2H), 2.74(t,J=4.4Hz,4H), 3.05-3.10(m,1H), 3.51-3.58(m,6H), 4.06-4.09(m,2H), 6.83(dd,J=3.6,0.4Hz,1H), 7.40(ddd,J=8.4,8.0,1.2Hz,1H), 7.48(d,J=3.6Hz,1H), 7.49(s,1H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.02(d,J=8.0Hz,1H).

Example 167 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline dihydrochloride

(167-1) 4-Methyl-5-(2-benzyloxyethyl)thiazole

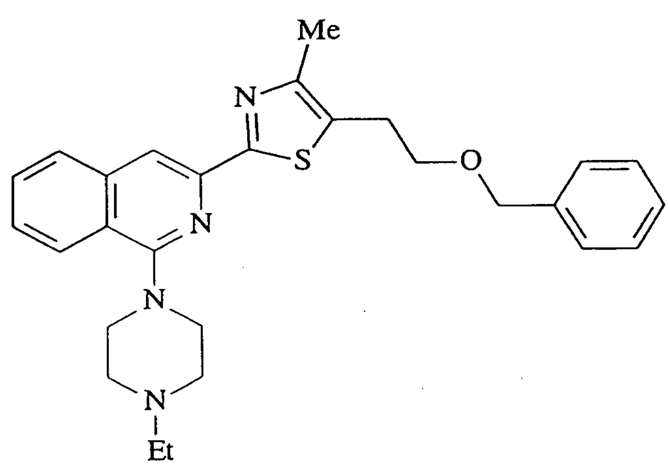



2-(4-Methyl-5-thiazolyl)ethanol (25.71 g) was dissolved in tetrahydrofuran (200 ml), followed by the addition of 60% sodium hydride (7.185 g) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hr. Thereafter,

the it was ice-cooled again, followed by the addition of benzyl bromide (21.4 ml) and tetrabutylammonium bromide (665 mg). The resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a yellow oil (39.059 g, yield; 93%).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 2.40(3H,s), 3.06(2H,t,J=6.6Hz), 3.66(2H,t,J=6.6Hz), 4.54(1H,s), 7.26-7.37(5H,m), 8.57(1H,s).

(167-2) 1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-benzyloxyethyl)thiazol-2-yl]isoquinoline

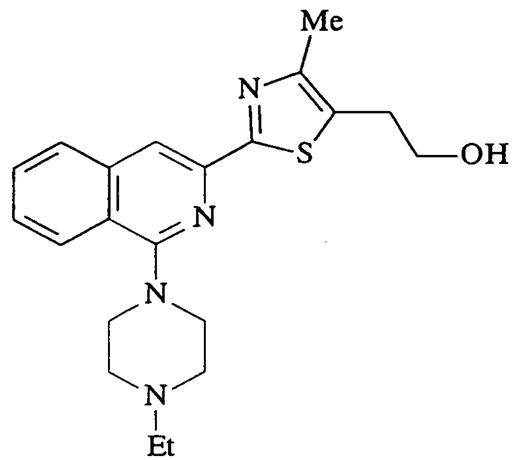



4-Methyl-5-(2-benzyloxyethyl)thiazole (2.333 g) was dissolved in tetrahydrofuran (20 ml), followed by the addition of 2.5 M n-butyl lithium (4 ml) in nitrogen atmosphere at -78°C, and the resulting mixture was stirred for 50 min. Tributyltin chloride (2.8 ml) was added thereto, and the mixture

was stirred for 1 hr. Sequentially, it was stirred at room temperature for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in xylene (30 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (506 mg) and tetrakis(triphenylphosphine)palladium (121 mg), and the resulting mixture was heated under stirring in nitrogen atmosphere at 120°C overnight. The reaction solution was diluted with ethyl acetate and extracted with 2N hydrochloric acid. The resulting aqueous layer was washed with ethyl acetate, basified with 8N sodium hydroxide, and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system), to give the title compound as a yellow oil (512 mg, yield; 69%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(3H,t,J=7.2Hz), 2.44(3H,s), 2.54(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.10(2H,t,J=6.6Hz), 3.57(4H,t,J=4.4Hz), 3.57(4H,t,J=4.4Hz), 3.72(2H,t,J=6.6Hz), 4.57(2H,s), 7.26-7.38(5H,m), 7.47(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,dd,J=8Hz,1.2Hz), 8.04(1H,s), 8.05(1H,dd,J=8Hz,1.2Hz).

<u>(167-3) 1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-hydroxyethyl)thiazol-2-yl]isoquinoline dihydrochloride</u>



1-(1-Ethylpiperazin-4-yl)-3-[4-methyl-5-(2-benzyloxyethyl)thiazol-2-yl]isoquinoline (512 mg) was converted into a hydrochloride, which was then dissolved in ethanol (7 ml), followed by the addition of palladium hydroxide (222 mg), and the mixture was stirred in hydrogen atmosphere at room temperature for 3 days. After palladium hydroxide was filtered off, the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale yellow crystals (129 mg, yield; 27%).

Hydrochloride:

m.p.; 149-154°C

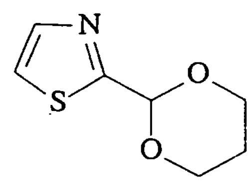
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 2.35(3H,s), 2.91(2H,t,J=6.4Hz), 3.15-3.24(2H,m), 3.30(1H,t,J=11.6Hz), 3.33(1H,t,J=11.6Hz), 3.47(2H,t,J=13.2Hz), 3.60(2H,d,J=11.6Hz), 3.60(2H,t,J=6.4Hz), 3.93(2H,d,J=13.2Hz),

7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,ddd,J=8Hz,7Hz,1.2Hz), 8.06(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.14(1H,s), 10.92(1H,br-s).

ESI-Mass ; 383($MH^+$).

Example 168 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline dihydrochloride

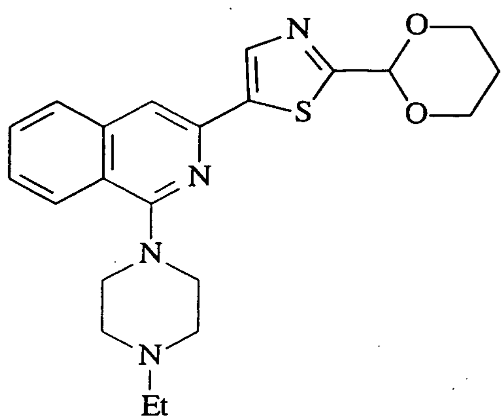
(168-1) 2-(1,3-Dioxan-2-yl)thiazole



2-Thiazolecarboxaldehyde (1 g) was dissolved in toluene (50 ml), followed by the addition of trimethylene glycol (3.36 g) and p-toluenesulfonic acid (17 mg). The resulting mixture was heated under reflux with a Dean-Stark apparatus for 4 hr. After cooling as it was, the reaction mixture was washed sequentially with an aqueous solution of saturated sodium bicarbonate and brine, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a brown solid (1.104 g, yield; 73%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.45-1.53(1H,m), 2.20-2.34(1H,m), 4.00-4.08(2H,m), 4.26-4.34(2H,m), 5.91(1H,s), 7.38(1H,d,J=3.2Hz), 8.01(1H,d,J=3.2Hz).

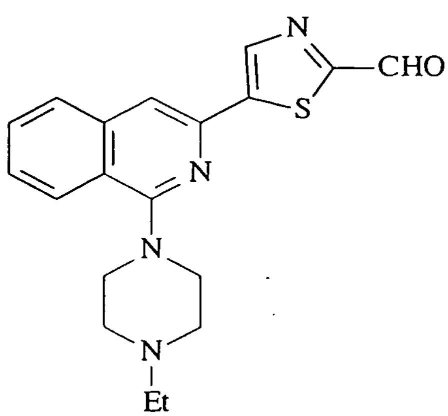
(168-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(1,3-dioxan-2-yl)thiazol-5-yl]isoquinoline



In the same manner as in Example 167-2, the title compound was obtained as a yellow oil (231 mg, yield; 35%) from 2-(1,3-dioxan-2-yl)thiazole (1.104 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (538 mg).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(3H,t,J=7.2Hz), 1.47-1.53(1H,m), 2.50-2.56(1H,m), 2.54(2H,q,J=7.2Hz), 2.72(4H,t,J=4.8Hz), 3.57(4H,t,J=4.8Hz), 4.02-4.10(2H,m), 4.30-4.36(2H,m), 5.80(2H,s), 7.46(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(1H,s), 7.59(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.74(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.25(1H,s).

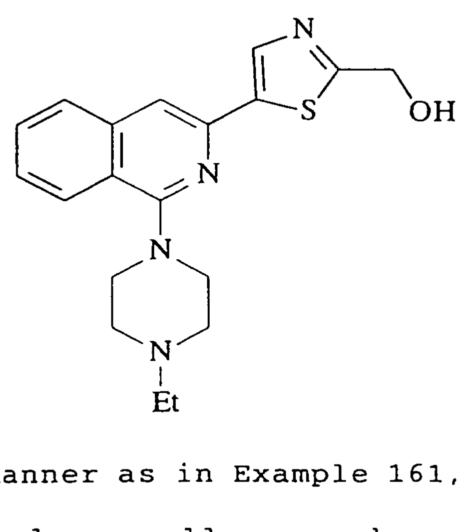
(168-3) 1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiazol-5-yl)isoquinoline



1-(1-Ethylpiperazin-4-yl)-3-[2-(1,3-dioxan-2-yl)thiazol-5-yl]isoquinoline (205 mg) was dissolved in tetrahydrofuran (4 ml), followed by the addition of 1N hydrochloric acid (3 ml), and the resulting mixture was stirred at room temperature for 8 hr. The reaction solution was basified by adding 8N sodium hydroxide thereto, and then extracted with in ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated, to give the title compound as a colorless oil (155 mg, yield; 80%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(3H,t,J=7.2Hz), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.8Hz), 3.60(4H,t,J=4.8Hz), 7.53(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.81(1H,d,J=8Hz), 8.06(1H,d,J=8Hz), 8.56(1H,s), 9.99(1H,s).

(168-4) 1-(1-Ethylpiperazin-4-yl)-3-(2-hydroxymethylthiazol-5-yl)isoquinoline dihydrochloride



In the same manner as in Example 161, the hydrochloride of the title compound as a yellow amorphous (79 mg, yield; 82%) from 1-(1-ethylpiperazin-4-yl)-3-(2-formylthiazol-5-

yl)isoquinoline (205 mg).

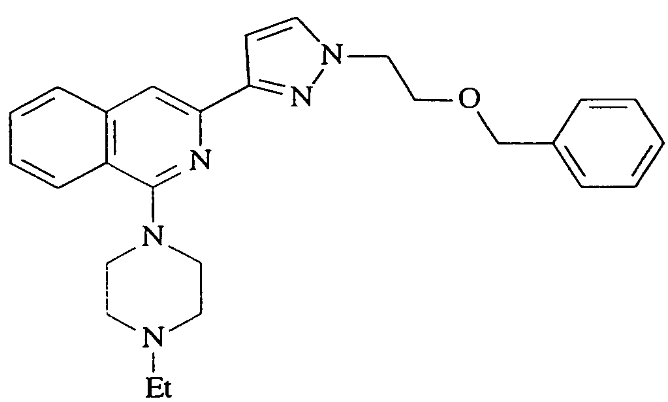
Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 3.15-3.23(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.49(2H,t,J=13.2Hz), 3.58(2H,d,J=11.6Hz), 3.94(2H,d,J=13.2Hz), 4.73(2H,s), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.90(1H,d,J=8Hz), 7.98(1H,s), 8.07(1H,d,J=8Hz), 8.35(1H,d,J=2Hz), 11.00(1H,br-s).

ESI-Mass; 355($MH^+$).

Example 169 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline dihydrochloride

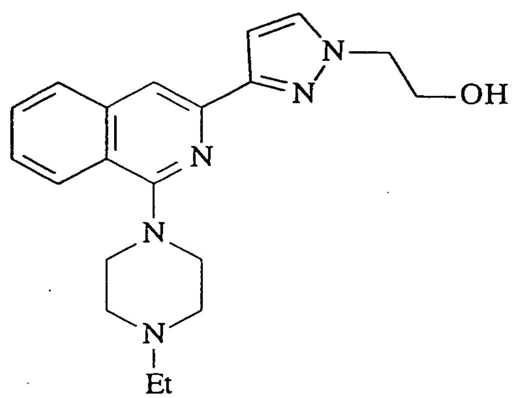
(169-1) 1-(1-Ethylpiperazin-4-yl)-3-[1-(2-benzyloxyethyl)pyrazol-3-yl]isoquinoline




In the same manner as in Example 167-2, the title compound was obtained as a yellow oil (386 mg, yield; 87%) from 1-(2-benzyloxyethyl)-3-bromopyrazole (1.144 g) described in Production Example 42 of JP-A 9-984331 and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (320 mg).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.17(3H,t,J=7.2Hz), 2.55(2H,q,J=7.2Hz), 2.74(4H,t,J=4.4Hz), 3.53(4H,t,J=4.4Hz), 3.89(2H,t,J=5.4Hz), 4.38(2H,t,J=5.4Hz), 4.51(2H,s), 7.24-7.36(5H,m), 7.38(1H,s), 7.40(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.04(1H,s), 8.08(1H,s).

<u>(169-2) 1-(1-Ethylpiperazin-4-yl)-3-[1-(2-hydroxyethyl)pyrazol-3-yl]isoquinoline dihydrochloride</u>



In the same manner as in Example 167, the hydrochloride of the title compound was obtained as pale yellow crystals (340 mg, yield; 92%) from 1-(1-ethylpiperazin-4-yl)-3-[1-(2-benzyloxyethyl)pyrazol-3-yl]isoquinoline (386 mg).

Hydrochloride:

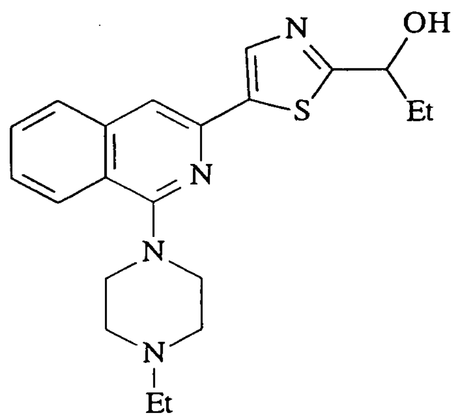
m.p.; 134-140°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.14-3.25(2H,m), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.49(2H,t,J=13.2Hz), 3.57(2H,d,J=11.2Hz), 3.76(2H,t,J=5.6Hz), 3.91(2H,d,J=13.2Hz), 4.19(2H,t,J=5.6Hz), 7.50(1H,dd,J=8Hz,7Hz), 7.67(1H,dd,J=8Hz,7Hz), 7.70(1H,s),

7.83(1H,d,J=8Hz), 8.03(1H,d,J=8Hz), 8.04(1H,s), 8.26(1H,s).

ESI-Mass; 352($MH^+$).

Example 170 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[(1-hydroxypropyl)thiazol-5-yl]isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-(2-formylthiazol-5-yl)isoquinoline (205 mg) was dissolved in tetrahydrofuran (2 ml), 1M ethylmagnesium bromide/tetrahydrofuran solution (0.26 ml) was added thereto under ice-cooling. The resulting mixture was stirred overnight. An aqueous solution of saturated ammonium chloride was added to the reaction solution, which was then extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (toluene/acetone system). The resulting product was converted into a hydrochloride in a conventional manner, and then solidified by adding ether thereto, to give the hydrochloride of the title compound as a brown amorphous (20 mg, yield; 23%).

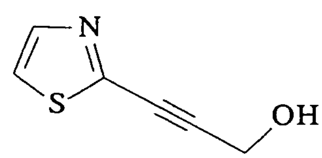
Hydrochloride:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 0.91(3H,t,J=7.6Hz), 1.29(3H,t,J=7.2Hz), 1.68-1.92(2H,m), 3.15-3.23(2H,m), 3.28(1H,t,J=11.6Hz), 3.31(1H,t,J=11.6Hz), 3.48(2H,t,J=13.6Hz), 3.58(2H,d,J=11.6Hz), 3.94(2H,d,J=13.6Hz), 4.71-4.75(1H,m), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.90(1H,d,J=8Hz), 7.97(1H,s), 8.07(1H,d,J=8Hz), 8.33(1H,s), 10.95(1H,br-s).

ESI-Mass; 383(MH$^+$).

Example 171 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline oxalate

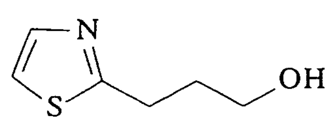
(171-1) 2-(2-Hydroxy-1-propynyl)thiazole



In the same manner as in Example 139-1, the title compound was obtained as a brown oil (8.596 g, yield; 75%) from 2-bromothiazole (13.547 g) and propargyl alcohol (5 ml).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 4.55(2H,s), 7.36(1H,d,J=3.4Hz), 7.81(1H,d,J=3.4Hz).

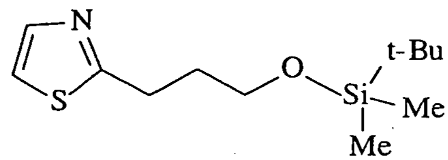
(171-2) 2-(3-Hydroxypropyl)thiazole



In the same manner as in Example 139-2, the title compound was obtained as a yellow oil (2.173 g, yield; 24%) from 2-(3-hydroxy-1-propynyl)thiazole (8.594 g).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 2.02-2.09(2H,m), 3.18(2H,t,J=7Hz), 3.44(1H,br-s), 3.74(2H,t,J=6Hz), 7.20(1H,d,J=3.4Hz), 7.67(1H,d,J=3.4Hz).

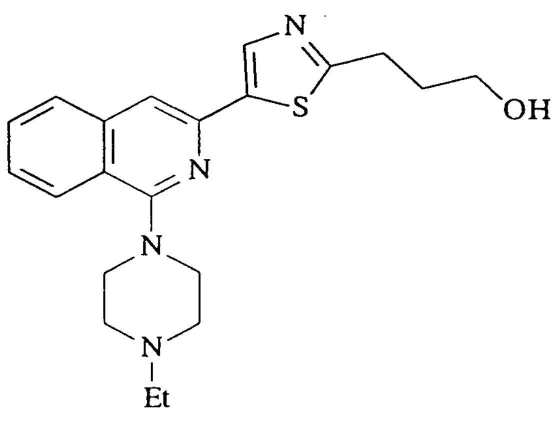
(171-3) 2-[3-(t-Butyldimethylsilyloxy)propyl]thiazole



In the same manner as in Example 163-1, the title compound was obtained as a colorless oil (3.792 g, yield; 98%) from 2-(3-hydroxypropyl)thiazole (2.173 g).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 0.05(6H,s), 0.90(9H,s), 1.99-2.06(2H,m), 3.11(2H,t,J=7.6Hz), 3.70(2H,t,J=6Hz), 7.19(1H,d,J=3.6Hz), 7.67(1H,d,J=3.6Hz).

(171-4) 1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline oxalate



In the same manner as in Example 167-2, the oxalate of the title compound was obtained as a pale yellow amorphous (221 mg, yield; 25%) from 2-[3-(t-butyldimethylsilyloxy)propyl]thiazole (3.792 g) and 1-(1-

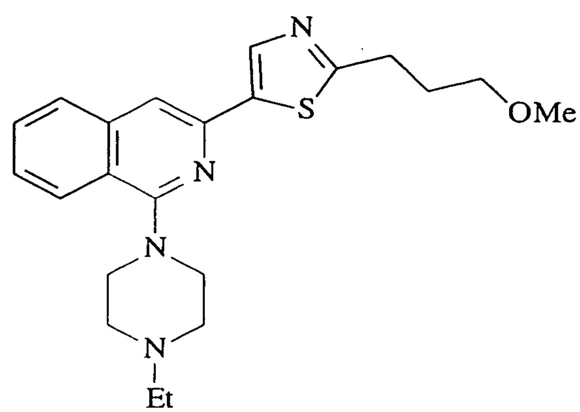
ethylpiperazin-4-yl)-3-bromoisoquinoline (631 mg).

Oxalate:

$^1H$-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 1.84-1.93(2H,m), 3.02(2H,t,J=7.6Hz), 3.10(2H,q,J=7.2Hz), 3.28-3.38(4H,m), 3.48(2H,t,J=6.4Hz), 3.54-3.70(4H,m), 7.58(1H,dd,J=8Hz,7Hz), 7.90(1H,d,J=8Hz), 7.94(1H,s), 8.07(1H,d,8Hz), 8.29(1H,s).

ESI-Mass; 383($MH^+$).

<u>Example 172 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(3-methoxypropyl)thiazol-5-yl]isoquinoline oxalate</u>



1-(1-Ethylpiperazin-4-yl)-3-[2-(3-hydroxypropyl)thiazol-5-yl]isoquinoline (95 mg) was dissolved in tetrahydrofuran (1 ml), followed by the addition of 60% sodium hydride (10 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 40 min. The reaction solution was ice-cooled again, followed by the addition of methyl iodide (17 ml), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The

resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). Then, the resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a colorless amorphous (12 mg, yield; 10%).

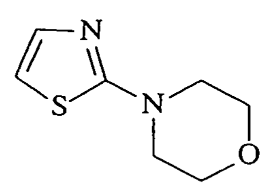
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(3H,t,J=7.2Hz), 1.93-2.00(2H,m), 3.02(2H,t,J=7.6Hz), 3.07(2H,q,J=7.2Hz), 3.24(3H,s), 3.25-3.36(4H,br-s), 3.39(2H,t,J=6.4Hz), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.91(1H,d,J=8Hz), 7.94(1H,s), 8.07(1H,d,J=8Hz), 8.30(1H,s).

ESI-Mass; 397($MH^+$).

Example 173 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)-5-thiazolyl]isoquinoline dihydrochloride

(173-1) 2-(4-Morpholinyl)thiazole

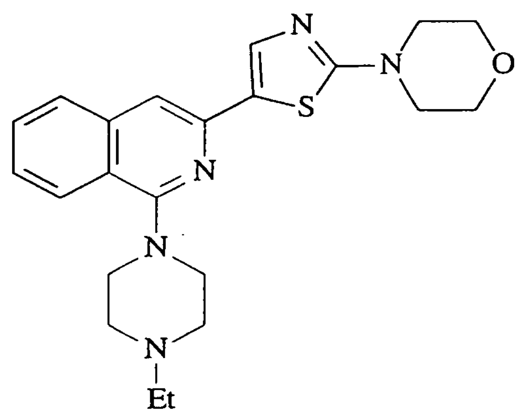


2-Bromothiazole (4.592 g) was added to morpholine (24 ml), and the mixture was stirred at 100°C for 4 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a pale yellow oil (4.531 g, yield;

95%).

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 3.47(4H,t,J=4.8Hz), 3.83(4H,t,J=4.8Hz), 3.61(2H,d,J=3.8Hz), 7.22(2H,d,J=3.8Hz).

(173-2) 1-(1-Ethylpiperazin-4-yl)-3-[2-(4-morpholinyl)-5-thiazolyl]isoquinoline dihydrochloride



In the same manner as in Example 167-2, the hydrochloride of the title compound was obtained as colorless crystals (recrystallized in ethanol/isopropyl ether) (728 mg, yield; 97%) from 2-(4-morpholinyl)thiazole (1.702 g) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (543 mg).

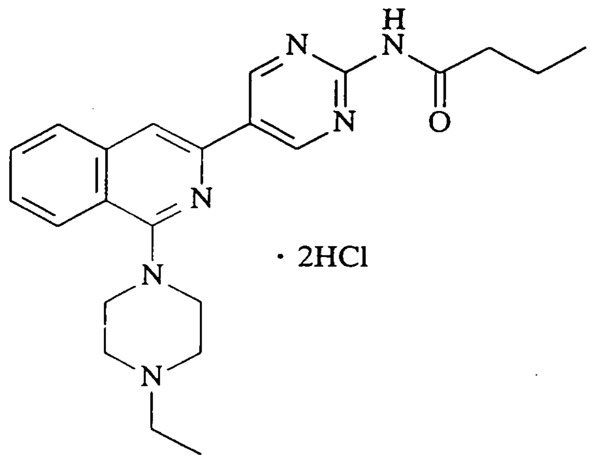
Hydrochloride:

m.p.; 265°C (decomp.)

$^1$H-NMR(400MHz, DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.28(1H,t,J=11.2Hz), 3.31(1H,t,J=11.2Hz), 3.46(2H,t,J=13.2Hz), 3.56(4H,t,J=4.8Hz), 3.57(2H,d,J=11.2Hz), 3.75(4H,t,J=4.8Hz), 3.89(2H,d,J=13.2Hz), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.84(1H,dd,J=8Hz,1.2Hz), 7.89(1H,s), 8.04(1H,s), 8.05(1H,dd,J=8Hz,1.2Hz), 11.40(1H,br-s).

ESI-Mass; 410($MH^+$).

<u>Example 174 Synthesis of 3-(2-propylcarbonylaminopyrimidin-5-yl)-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride</u>



In the same manners sequentially as in Examples 161-2 and 20, the free compound of the title compound was obtained (60 mg, yield; 13%) from 5-bromo-2-propylcarbonylaminopyridine (2.73 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (363 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 216-219°C

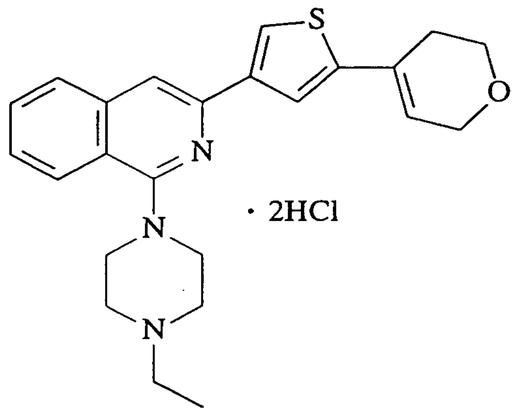
MS(FAB) m/z 405($M+H$)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.06(t,J=7.2Hz,3H), 1.17(t,J=7.6Hz,3H), 1.77-1.86(m,2H), 2.55(q,J=7.2Hz,2H), 2.74(br,6H), 3.60(br,4H), 7.51(d,J=8.0,1.2Hz,1H), 7.63(dt,J=8.0,1.2Hz,1H), 7.63(s,1H), 7.81(d,J=8.0Hz,1H),

8.08(d,J=8.0Hz,1H), 9.32(s,2H).

Example 175 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-4-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride




In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (310 mg, yield; 82%) from 4-bromo-2-(5,6-dihydro-2H-pyran-4-yl)thiophene (650 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 190-193°C

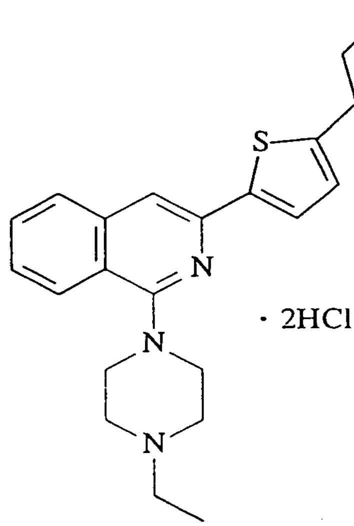
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.20-3.28(m,2H), 3.30-3.38(m,2H), 3.45-3.52(m,2H), 3.59-3.63(m,2H), 3.83-3.87(m,2H), 3.96-4.02(m,4H), 4.23(d,J=2.8Hz,2H), 6.23(s,1H), 7.59(t,J=8.0Hz,1H), 7.74(t,J=8.0Hz,1H), 7.78(s,1H), 7.91(d,J=8.0Hz,1H), 7.95(s,1H), 8.05(s,1H), 8.09(d,J=8.0Hz,1H).

MS(FAB) m/z 406(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz, $CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.25(q,J=7.2Hz,2H), 2.61-2.63(m,2H), 2.75(br,4H), 3.56(br,4H), 3.94-3.97(m,2H), 4.32-4.34(m,2H), 6.17(br,1H), 7.44(t,J=8.4Hz,1H), 7.50(s,1H), 7.57(t,J=8.4Hz,1H), 7.58(s,1H), 7.75(d,J=8.4Hz,1H), 7.84(s,1H), 8.05(d,J=8.4Hz,1H).

Example 176 Synthesis of 3-[2-(5,6-dihydro-2H-pyran-4-yl)thiophen-5-yl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manners sequentially as in Examples 161-2 and 20, a yellow compound was obtained (120 mg, yield; 32%) from 5-bromo-2-(5,6-dihydro-2H-pyran-4-yl)thiophene (632 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (300 mg). The resulting compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title

compound as yellow crystals.

Hydrochloride:

m.p.; 256-258°C

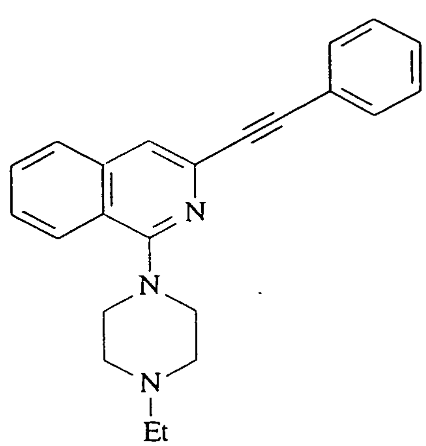
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(t,J=7.2Hz,3H), 3.23(br,2H), 3.33(br,4H), 3.48(br,2H), 3.61(br,2H), 3.83(t,J=6.4Hz,2H), 3.96(d,J=13.2Hz,2H), 4.23(br,2H), 6.25(br,1H), 7.16(d,J=3.6Hz,1H), 7.57(t,J=8.0Hz,1H), 7.71(d,J=3.6Hz,1H), 7.73(t,J=8.0Hz,1H), 7.92(d,J=8.0Hz,1H), 7.92(d,J=8.0Hz,1H), 7.95(s,1H), 8.08(d,J=8.0Hz,1H).

MS(FAB) m/z 406(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.17(t,J=7.2Hz,3H), 2.52-2.57(m,2H), 2.54(q,J=7.2Hz,2H), 2.74(br,4H), 3.57(br,4H), 3.94(t,J=5.6Hz,2H), 4.40(q,J=2.8Hz,2H), 6.21(br,1H), 6.99(d,J=3.6Hz,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.52(s,1H), 7.53(d,J=3.6Hz,1H), 7.56(ddd,J=8.4,8.0,1.2Hz,1H), 7.72(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 177 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(phenylethynyl)isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (357 mg) was dissolved in triethylamine (6 ml), followed by the addition of phenylacetylene (132 ml), copper iodide (4 mg) and bis(triphenylphosphine)palladium (II) chloride (14 mg), and the resulting mixture was stirred in nitrogen atmosphere at room temperature overnight, and then stirred at 50°C for 6 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as yellow crystals (270 mg, yield; 58%).

Hydrochloride:

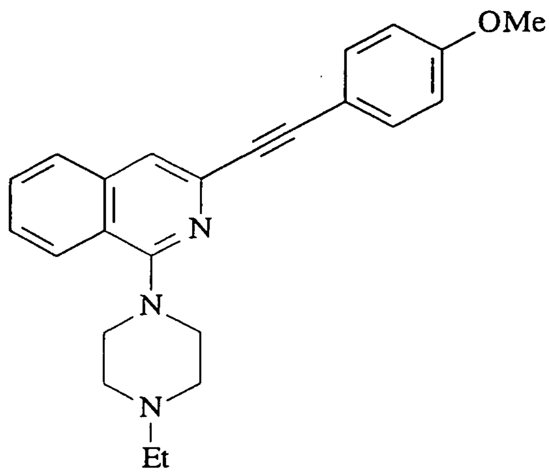
m.p.; 133-136°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.29(1H,t,J=11.2Hz), 3.32(1H,t,J=11.2Hz), 3.49(2H,t,J=13.6Hz), 3.57(2H,d,J=11.2Hz), 3.85(2H,d,J=13.6Hz), 7.42-7.47(3H.m), 7.59-7.63(2H,m), 7.66(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.77(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.83(1H,s), 7.95(1H,d,J=8Hz), 8.12(1H,d,J=8Hz), 11.35(1H,br-s).

ESI-Mass; 342($MH^+$).

Example 178 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-

methoxyphenyl)ethynylisoquinoline dihydrochloride



In the same manner as in Example 177, the hydrochloride of the title compound was obtained as yellow crystals (recrystallized from ethanol/isopropyl ether) (437 mg, yield; 77%) from 4-methoxyphenylacetylene (185 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (370 mg).

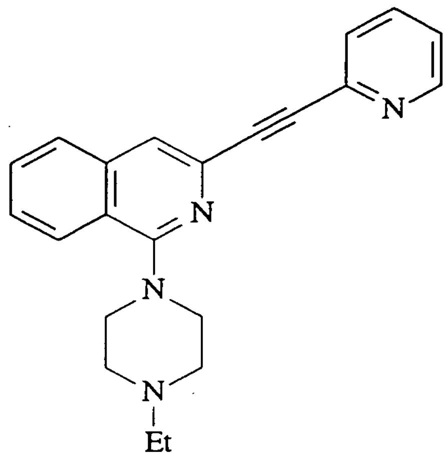
Hydrochloride:

m.p.; 230°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.29(1H,t,J=11.6Hz), 3.32(1H,t,J=11.6Hz), 3.42(2H,t,J=12.8Hz), 3.58(2H,d,J=11.6Hz), 3.80(3H,s), 3.86(2H,d,J=12.8Hz), 7.00(2H,d,J=8.8Hz), 7.55(2H,d,J=8.8Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,s), 7.93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz).

ESI-Mass; 372(MH$^+$).

Example 179 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2-pyridyl)ethynylisoquinoline oxalate



In the same manner as in Example 177, the oxalate of the title compound was obtained as a yellow amorphous (437 mg, yield; 77%) from 2-ethynylpyridine (157 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (425 mg).

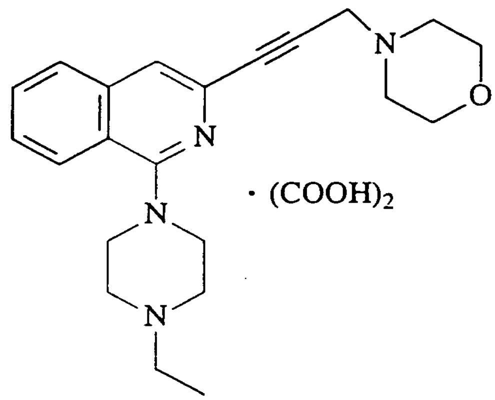
Hydrochloride:

m.p.; 148-154°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2H), 3.10(2H,q,J=7.2Hz), 3.27-3.38(4H,br-s), 3.50-3.66(4H,br-s), 7.44(1H,ddd,J=7.8Hz,4.8Hz,1.2Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.70(1H,ddd,J=7.8Hz,1.2Hz,0.8Hz), 7.78(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.7(1H,ddd,J=7.8Hz,7.8H,1.6Hz), 7.96(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 8.63(1H,ddd,J=4.8Hz,1.6Hz,0.8Hz).

ESI-Mass; 343(MH$^+$).

<u>Example 180 Synthesis of 3-[3-(4-morpholinyl)-1-propynyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate</u>



In the same manner as in Example 177, the free compound of the title compound was obtained (485 mg, yield; 77%) from 4-propargyl morpholine (819 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (552 mg). The resulting free compound was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 231-233°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.28(t,J=7.2Hz,3H), 2.66(t,J=4.8Hz,2H), 3.23(q,J=7.2Hz,2H), 3.46(br,6H), 3.66-3.69(m,8H), 7.66(ddd,J=8.4,8.0,1.2Hz,1H), 7.73(s,1H), 7.77(ddd,J=8.4,8.0,1.2Hz,1H), 7.94(d,J=8.0Hz,1H), 8.12(d,J=8.4Hz,1H).

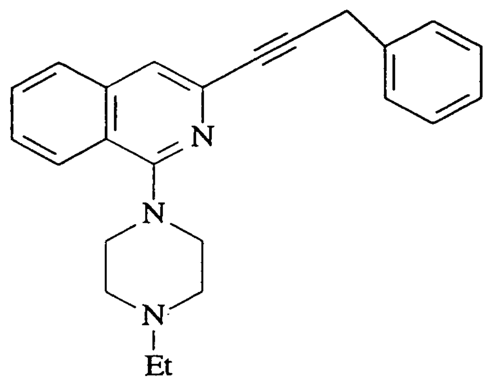
MS(FAB) m/z 365(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.15-1.18(m,3H), 2.57(br,2H), 2.69(t,J=4.8Hz,4H), 2.74(br,4H), 3.51(t,J=4.8Hz,4H), 3.59(s,2H), 3.79(t,J=4.8Hz,4H), 7.45(s,1H),

7.49(ddd,J=8.4,8.0,1.2Hz,1H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.68(d,J=8.0Hz,1H), 8.03(d,J=8.4Hz,1H).

Example 181 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(3-phenyl-1-propynyl)isoquinoline oxalate




In the same manner as in Example 177, the oxalate of the title compound was obtained as brown crystals (recrystallized from ethanol/isopropyl ether) (468 mg, yield; 73%) from 3-phenyl-1-propyne (268 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (493 mg).

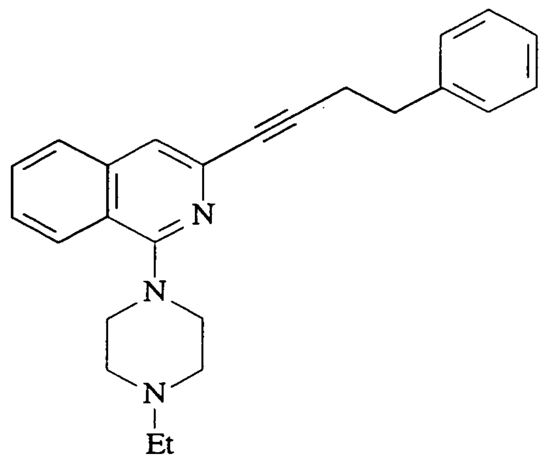
Oxalate:

m.p.; 180-183°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.22(3H,t,J=7.2Hz), 3.09(2H,q,J=7.2Hz), 3.26-3.36(4H,m), 3.46-3.58(4H,m), 3.94(2H,s), 7.23-7.29(1H,m), 7.33-7.44(4H,m), 7.62(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.67(1H,s), 7.73(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(1H,d,J=8Hz), 8.07(1H,d,J=8Hz).

ESI-Mass; 356(MH$^+$).

Example 182 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(4-phenyl-1-butynyl)isoquinoline dihydrochloride



In the same manner as in Example 177, the hydrochloride of the title compound was obtained as brown crystals (recrystallized from ethanol/isopropyl ether) (468 mg, yield; 73%) from 4-phenyl-1-butyne (302 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (474 mg).

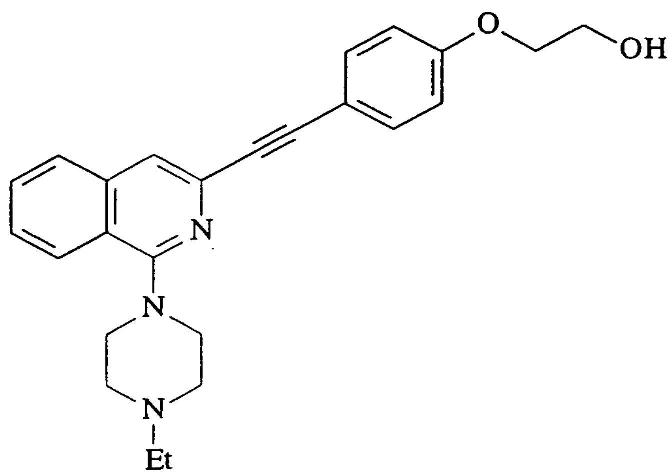
Hydrochloride:

m.p.; 120-128°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 2.75(3H,t,J=7.4Hz), 2.88(2H,t,J=7.4Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.26(1H,t,J=11.6Hz), 3.29(1H,t,J=11.6Hz), 3.40(2H,t,J=13.2Hz), 3.56(2H,d,J=11.6Hz), 3.81(2H,d,J=13.2Hz), 7.19-7.23(1H,m), 7.28-7.34(4H,m), 7.56(1H,s), 7.61(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.72(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.88(11H,d,J=8Hz), 8.07(1H,d,J=8Hz), 11.00(1H,br-s).

ESI-Mass; 370(MH$^+$).

<u>Example 183 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[4-(2-hydroxyethoxy)phenylethynyl]isoquinoline dihydrochloride</u>



4-Iodophenol (11.041 g) was dissolved in N,N-dimethylformamide (100 ml), followed by the addition of 60% sodium hydride (2.2 g) under ice-cooling, and the mixture was stirred at room temperature for 30 min. Subsequently, the mixture was ice-cooled again, followed by the addition of (2-bromoethoxy)-t-butyldimethylsilane (13.158 g), and the mixture was stirred at room temperature for 2 hr. Then the mixture was stirred at 80°C for further 2 hr. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue and (trimethylsilyl)acetylene (6 g) were treated in the same manner as in Example 139-1. The reaction mixture was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in tetrahydrofuran (50 ml), followed by the addition of 5N hydrochloric acid (25 ml), and the resulting mixture was stirred for 30 min. Then, it was

extracted with ethyl acetate and evaporated. The resulting residue was dissolved in methanol (15 ml), followed by the addition of 1N sodium hydroxide (5 ml), and the mixture was stirred at room temperature for 2 hr. The resulting mixture was evaporated, and the resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. From the product obtained by the same treatment as in Example 177 and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (419 mg), the hydrochloride of the title compound was obtained as yellow crystals (recrystallized in ethanol/isopropyl ether) (328 mg, yield; 54%).

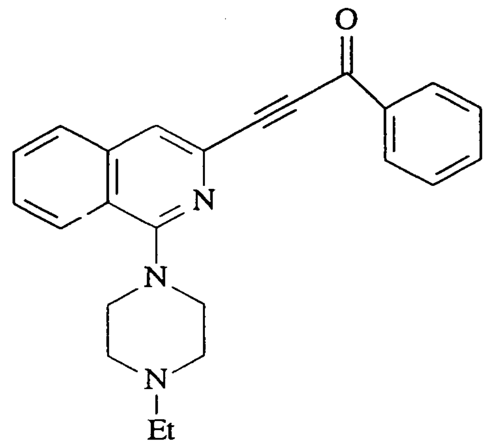
Hydrochloride:

m.p.; 205-208°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.19(1H,q,J=7.2Hz), 3.21(1H,q,J=7.2Hz), 3.29(1H,t,J=10.8Hz), 3.32(1H,t,J=10.8Hz), 3.45(2H,t,J=13.6Hz), 3.58(2H,d,J=10.8Hz), 3.71(2H,t,J=4.8Hz), 3.85(2H,d,J=13.6Hz), 4.03(2H,t,J=4.8Hz), 7.00(2H,d,J=8.8Hz), 7.54(2H,d,J=8.8Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.78(1H,s), 7.93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz), 11.02(1H,br-s).

ESI-Mass; 402($MH^+$).

Example 184 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-benzoylethynylisoquinoline oxalate



1-(1-Ethylpiperazin-4-yl)-3-(3-hydroxy-3-phenyl-1-propynyl)isoquinoline (400 mg) was dissolved in chloroform (30 ml), followed by the addition of manganese dioxide (4.038 g), and the resulting mixture was stirred at room temperature for 1 hr. After the manganese dioxide was filtered off, the resulting solution was evaporated, and the resulting residue was purified by silica gel column chromatography (ethyl acetate/acetone system). The resulting product was converted into an oxalate in a conventional manner, and then recrystallized from ethanol, to give the oxalate of the title compound as brown crystals (358 mg, yield; 73%).

Oxalate:

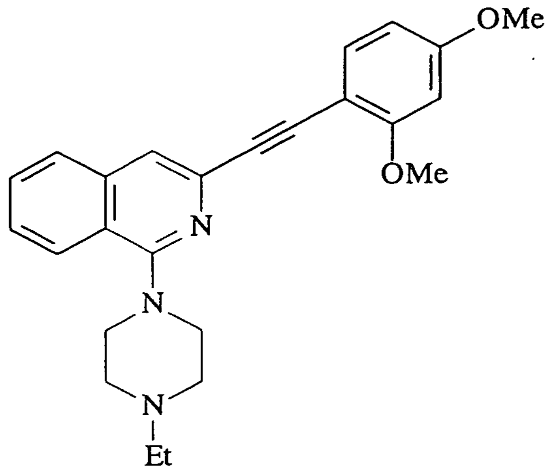
m.p.; 161-163°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.23(3H,t,J=7.2Hz), 3.07(2H,q,J=7.2Hz), 3.25-3.35(4H,m), 3.54-3.68(4H,m), 7.63-7.68(2H,m), 7.74-7.87(3H,m), 8.06(1H,d,J=8Hz), 8.16(1H,d,J=8Hz), 8.19-8.22(3H,m).

ESI-Mass; 370(MH$^+$).

<u>Example 185 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(2,4-</u>

dimethoxyphenylethynyl)isoquinoline dihydrochloride



1-Bromo-2,4-dimethoxybenzene (2.18 g) was dissolved in triethylamine (20 ml), followed by the addition of (trimethylsilyl)acetylene (1.092 g), copper iodide (38 mg) and bis(triphenylphosphine)palladium (II) chloride (140 mg), and the resulting mixture was stirred in nitrogen atmosphere at 50°C overnight. The resulting insoluble matters were filtered off from the reaction mixture, which was then evaporated. The resulting residue was dissolved in methanol (50 ml), followed by the addition of 1N sodium hydroxide (20 ml), and the mixture was stirred at room temperature for 1 hr. Subsequently, it was evaporated. The resulting residue was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. Then, the resulting residue was dissolved in triethylamine (15 ml), followed by the addition of 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (415 mg), cooper iodide (5 mg) and bis(triphenylphosphine)palladium (II) chloride (18 mg), and

the resulting mixture was stirred in nitrogen atmosphere at 50°C overnight. The resulting insoluble matters were filtered off from the reaction mixture, which was then evaporated. Ethyl acetate was added to the resulting residue, and then the mixture was extracted with 2N hydrochloric acid. The resulting aqueous layer was basified with 8N sodium hydroxide and extracted with ethyl acetate. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and then recrystallized (from ethanol/isopropyl ether), to give the hydrochloride of the title compound as yellow crystals (161 mg, yield; 31%).

Hydrochloride:

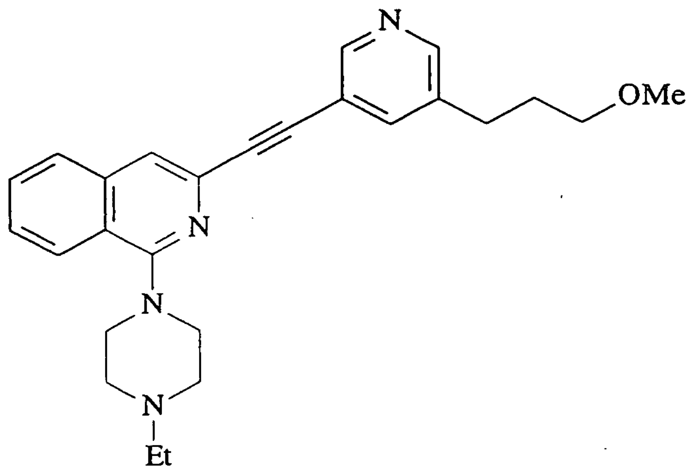
m.p.; 123-129°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.30(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.29(1H,t,J=10.8Hz), 3.32(1H,t,J=10.8Hz), 3.42(2H,t,J=12.8Hz), 3.58(2H,d,J=10.8Hz), 3.81(3H,s), 3.82(2H,d,J=12.8Hz), 3.86(3H,s), 6.58(1H,dd,J=8.4Hz.2.4Hz), 7.45(1H,d,J=8.4Hz), 7.63(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.73(1H,s), 7.75(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.93(1H,d,J=8Hz), 8.10(1H,d,J=8Hz), 10.90(1H,br-s).

ESI-Mass; 420($MH^+$).

Example 186 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(3-

methoxypropyl)-5-pyridyl]ethynylisoquinoline



In the same manner as in Example 185, the hydrochloride of the title compound was obtained as pale yellow crystals (recrystallized from ethanol/isopropyl ether) (361 mg, yield; 50%) from 5-bromo-3-(3-methoxypropyl)pyridine (470 mg), (trimethylsilyl)acetylene (390 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (345 mg).

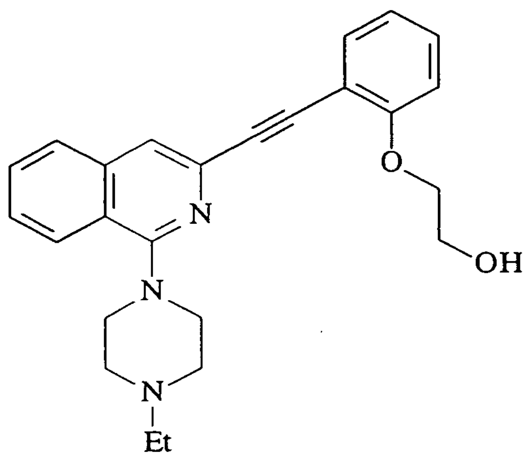
Hydrochloride:

m.p.; 135-140°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(3H,t,J=7.2Hz), 1.84-1.92(2H,m), 2.79(2H,t,J=7.8Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(3H,s), 3.29(1H,t,J=11.6Hz), 3.32(1H,t,J=11.6Hz), 3.33(2H,t,J=6.2Hz), 3.51(2H,t,J=13.2Hz), 3.57(2H,d,J=11.6Hz), 3.84(2H,d,J=13.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.80(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.92(1H,s), 7.99(1H,d,J=8Hz), 8:15(1H,d,J=8Hz), 8.47(1H,t,J=2Hz), 8.73(1H,d,J=2Hz), 8.97(1H,d,J=2Hz), 11.60(1H,br-s).

ESI-Mass; 415($MH^{+}$).

Example 187 Synthesis of 1-(1-Ethylpiperazin-4-yl)-3-[2-(2-hydroxyethoxy)phenyl]ethynylisoquinoline oxalate



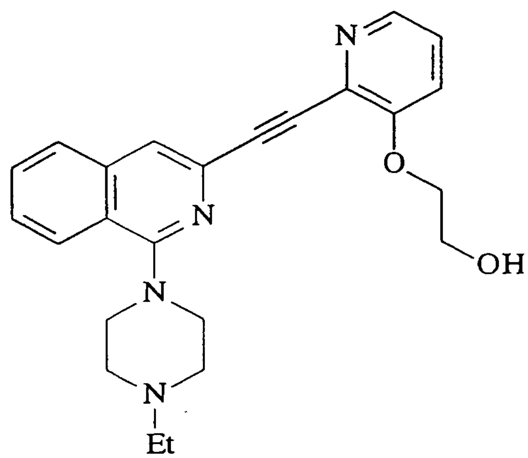
In the same manner as in Example 185, the oxalate of the title compound was obtained as a pale yellow amorphous (330 mg, yield; 54%) from 2-iodophenol (1.089 g), (2-bromoethoxy)-t-butyldimethylsilane (1.302 g), (trimethylsilyl)acetylene (579 mg) and 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (408 mg).

Oxalate:

$^{1}$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(3H,t,J=7.2Hz), 3.11(2H,q,J=7.2Hz), 3.30-3.38(4H,m), 3.33-3.48(1H,m), 3.50-3.66(4H,m), 3.78(2H,t,J=5.2Hz), 4.12(2H,t,J=5.2Hz), 6.98(1H,ddd,J=7.6Hz,7.6Hz,1.6Hz), 7.65(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.75(1H,s), 7.76(1H,ddd,J=8Hz,7Hz,1.2Hz), 7:93(1H,d,J=8Hz), 8.11(1H,d,J=8Hz).

ESI-Mass; 402($MH^{+}$).

Example 188 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[3-(2-hydroxyethoxy)-2-pyridyl]ethynylisoquinoline



In the same manner as in Example 185, the hydrochloride of the title compound was obtained as yellow crystals (261 mg, yield; 38%) from 2-bromo-3-hydroxypyridine (2.095 g), (2-bromoethoxy)-t-butyldimethylsilane (3.425 g), (trimethylsilyl)acetylene (613 mg) and 1-(1-ethylpiperazin-4-yl-3-bromoisoquinoline (410 mg).

Hydrochloride:

m.p.; 153-159°C

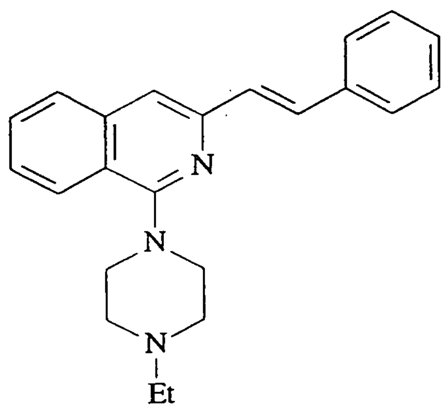
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.31(3H,t,J=7.2Hz), 3.18(1H,q,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.29(1H,t,J=10.2Hz), 3.32(1H,t,J=10.2Hz), 3.51(2H,t,J=13.2Hz), 3.58(2H,d,J=10.2Hz), 3.80(1H,t,J=5Hz), 3.90(2H,d,J=13.2Hz), 4.23(1H,t,J=5Hz), 7.55(1H,dd,J=8.4Hz,1.6Hz), 7.89(1H,s), 7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.26(1H,dd,J=4.6Hz,1.6Hz), 7.89(1H,s), 7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz), 8.26(1H,dd,J=4.6Hz,1.6Hz), 7.89(1H,s),

7.99(1H,d,J=8Hz), 8.13(1H,d,J=8Hz),

8.26(1H,dd,J=4.6Hz,1.6Hz), 11.55(1H,br-s).

ESI-Mass; 403($MH^+$).

Example 189 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-2-phenylethenyl)isoquinoline dihydrochloride



1-(1-Ethylpiperazin-4-yl)-3-bromoisoquinoline (702 mg) was dissolved in N,N-dimethylformamide (15 ml), followed by the addition of styrene (369 mg), palladium (II) acetate (49 mg), tri-o-tolylphosphine (134 mg) and triethylamine (5 ml), and the resulting mixture was stirred in nitrogen atmosphere at 100°C overnight. After the insoluble matters were filtered off, the resulting filtrate was evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system). The resulting product was converted into a hydrochloride in a conventional manner, and recrystallized from ethanol/isopropyl ether, to give the hydrochloride of the title compound as pale brown crystals (412 mg, yield; 45%).

Hydrochloride:

m.p.; 222-225°C

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.32(3H,t,J=7.2Hz),

3.21(1H,q,J=7.2Hz), 3.23(1H,q,J=7.2Hz), 3.33(1H,t,J=11.2Hz),

3.55(1H,t,J=11.2Hz), 3.49(2H,t,J=13.6Hz),

3.60(2H,d,J=11.2Hz), 3.96(2H,d,J=13.6Hz), 7.27-7.32(1H,m),

7.35(1H,d,J=15.6Hz), 7.40(2H,t,J=7.6Hz), 7.50(1H,s),

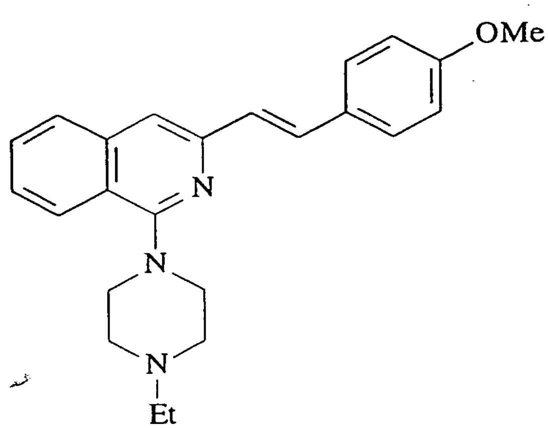
7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.65(2H,d,J=7.6Hz),

7.68(1H,d,J=15.6Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz),

7.89(1H,d,J=8Hz), 10.59(1H,br-s).

ESI-Mass; 344(MH$^+$).

Example 190 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(4-methoxyphenyl)ethenyl]isoquinoline dihydrochloride




In the same manner as in Example 189, the hydrochloride of the title compound was obtained as yellow crystals (450 mg, yield; 53%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (595 mg) and 4-methoxystyrene (382 mg).

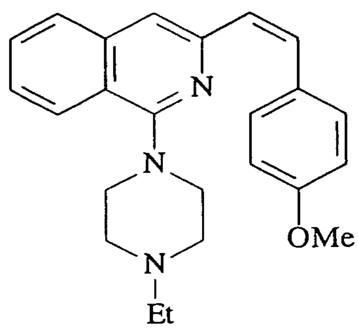
Hydrochloride:

m.p.; 227°C (decomp.)

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.32(3H,t,J=7.2Hz), 3.20(1H,q,J=7.2Hz), 3.22(1H,q,J=7.2Hz), 3.31(1H,t,J=11.6Hz), 3.34(1H,t,J=11.6Hz), 3.60(2H,d,J=11.6Hz), 3.78(3H,s), 3.95(2H,d,J=13.6Hz), 6.96(2H,d,J=8.8Hz), 7.20(1H,d,J=15.6Hz), 7.45(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.59(2H,d,J=8.8Hz), 7.63(1H,d,J=15.6Hz), 7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,dd,J=8Hz,1.2Hz), 8.06(1H,dd,J=8Hz,1.2Hz), 11.05(1H,br-s).

ESI-Mass; 374($MH^+$).

Example 191 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[cis-2-(4-methoxyphenyl)ethenyl]isoquinoline oxalate




1-(1-Ethylpiperazin-4-yl)-3-(4-methoxyphenylethynyl)isoquinoline (226 mg) was dissolved in ethanol (10 ml), followed by the addition of Lindlar catalyst (45 mg), and the resulting mixture was stirred in hydrogen atmosphere at room temperature for 25 min. After the catalyst was filtered off, the mixture was evaporated and partitioned between ethyl acetate and 1N sodium hydroxide. The resulting organic layer was washed with water, dried (over $MgSO_4$), evaporated, and then purified by (NH) silica gel column

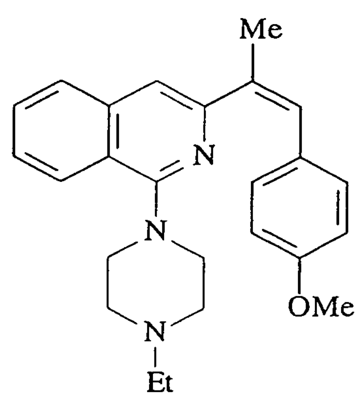
chromatography (ethyl acetate/hexane system). The resulting product was converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a yellow amorphous (137 mg, yield; 49%).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.02(3H,t,J=7.2Hz), 2.83(2H,q,J=7.2Hz), 2.94-3.04(4H,m), 3.14-3.28(4H,m), 3.58(3H,s), 6.40(1H,d,J=12.4Hz), 6.48(1H,d,J=12.4Hz), 6.68(1H,d,J=8.8Hz), 7.21(2H,d,J=8.8Hz), 7.22(1H,s), 7.39(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.50(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.63(1H,d,J=8Hz), 7.87(1H,d,J=8Hz).

ESI-Mass; 374($MH^+$).

Example 192 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(cis-1-methyl-2-phenylethenyl)isoquinoline oxalate



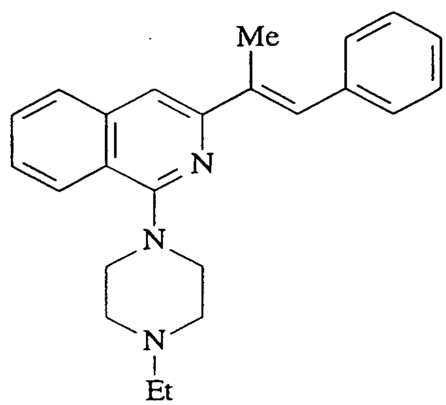

In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (465 mg, yield; 53%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (617 mg) and cis-$\beta$-methylstyrene (451 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.14(3H,t,J=7.2Hz), 2.25(3H,s), 3.01(2H,q,J=7.2Hz), 3.12-3.22(4H,m), 3.30-3.44(4H,m), 6.64(1H,s), 6.93(2H,d,J=7.6Hz), 7.04-7.12(3H,m), 7.29(1H,s), 7.5(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.76(1H,d,J=8Hz), 8.03(1H,d,J=8Hz).

ESI-Mass; 358(MH$^+$).

Example 193 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-1-methyl-2-phenylethenyl)isoquinoline



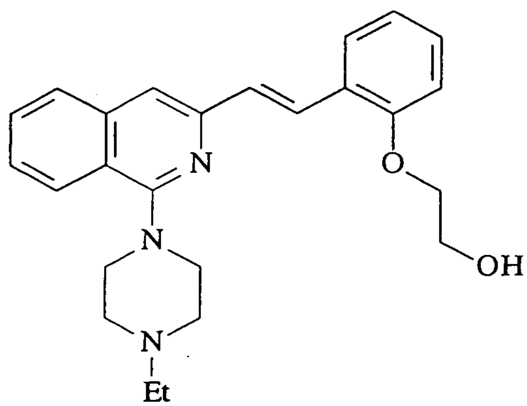

In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (576 mg, yield; 68%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (607 mg) and trans-$\beta$-methylstyrene (453 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(3H,t,J=7.2Hz), 2.31(3H,s), 3.12(2H,q,J=7.2Hz), 3.30-3.40(4H,m), 3.54-3.70(4H,m), 7.25-7.32(1H,m), 7.39-7.45(4H,m), 7.57(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,s), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.82(1H,s), 7.95(1H,dd,J=8Hz,1.2Hz), 8.08(1H,dd,J=8Hz,1.2Hz).

ESI-Mass; 358(MH$^+$).

Example 194 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-hydroxyethoxyphenyl)ethenyl]isoquinoline oxalate



The product obtained from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (700 mg) and 2-vinylphenoxyacetate n-butyl ester (486 mg) by the same treatment as in Example 189 was dissolved in tetrahydrofuran (6 ml), followed by the addition of lithium aluminium hydride (83 mg) under ice-cooling, and stirring for 5 min. To the reaction mixture were sequentially added water (85 ml), 5N sodium hydroxide (85 ml) and water (255 ml), the resulting insoluble matters were filtered off through Celite, and the resulting solution was evaporated. The resulting residue was purified by (NH) silica gel column chromatography (ethyl acetate/hexane system), and then converted into an oxalate in a conventional manner, to give the oxalate of the title compound as a yellow amorphous (248 mg, yield; 23%).

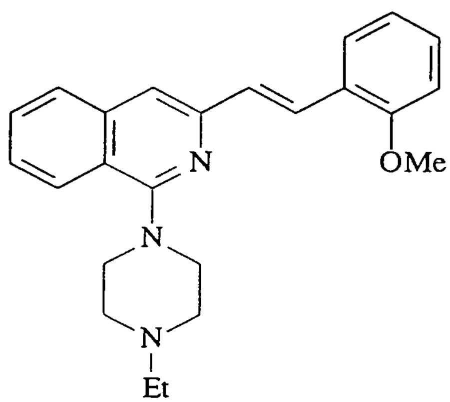
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz),

3.13(2H,q,J=7.2Hz), 3.30-3.42(4H,m), 3.60-3.80(4H,m), 3.82(2H,t,J=5Hz), 4.08(2H,t,J=5Hz), 6.98(1H,dd,J=7.6Hz,7.6Hz), 7.05(1H,d,J=8.2Hz), 7.26(1H,ddd,J=8.2Hz,7.6Hz,1.6Hz), 7.34(1H,d,J=16Hz), 7.42(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,dd,J=7.6Hz,1.6Hz), 7.87(1H,d,J=8Hz), 8.06(1H,d,J=16Hz), 8.06(1H,d,J=8Hz).

ESI-Mass; 404($MH^+$).

Example 195 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[trans-2-(2-methoxyphenyl)ethenyl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound obtained as a yellow amorphous (224 mg, yield; 31%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (507 mg) and 2-methoxystyrene (425 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.26(3H,t,J=7.2Hz), 3.16(2H,q,J=7.2Hz), 3.36-3.46(4H,m), 3.54-3.72(4H,m), 3.87(3H,s), 6.98(1H,t,J=7.6Hz), 7.06(1H,d,J=8.2Hz), 7.29(1H,ddd,J=8.2Hz,7.6Hz,1.6Hz), 7.30(1H,d,16Hz),

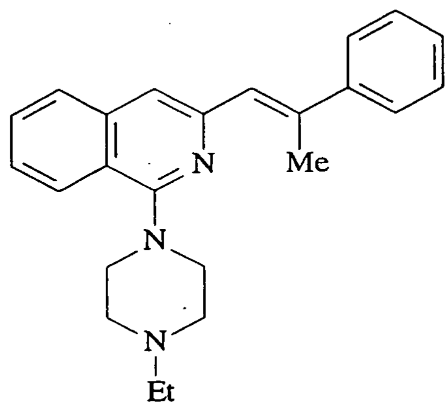
7.47(1H,s), 7.55(1H,ddd,J=8Hz,7Hz,1.2Hz),

7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.69(1H,dd,J=7.6Hz,1.6Hz),

7.88(1H,d,J=8Hz), 7.96(1H,d,J=16Hz), 8.07(1H,d,J=8Hz).

FAB-Mass; 376($MH^+$).

Example 196 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-(trans-2-methyl-2-phenylethen-1-yl)isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (371 mg, yield; 44%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (584 mg) and α-methylstyrene (425 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); δ (ppm) 1.23(3H,t,J=7.2Hz),

2.68(3H,d,J=1.2Hz), 3.08(2H,q,J=7.2Hz), 3.28-3.38(4H,m),

3.50-3.64(4H,m), 6.87(1H,d,J=1.2Hz), 7.28-7.34(1H,m),

7.40(2H,t,J=7.6Hz), 7.52(1H,s), 7.54-7.62(3H,m),

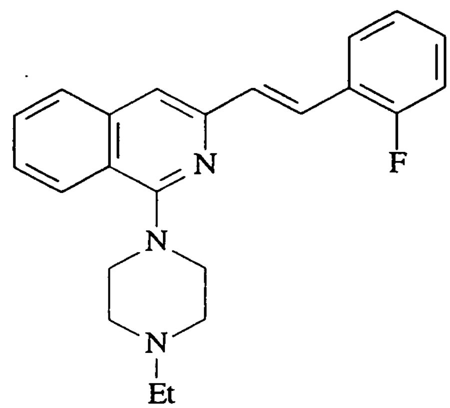
7.69(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.86(1H,d,J=8Hz),

8.08(1H,d,J=8Hz).

FAB-Mass; 368($MH^+$).

Example 197 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-

[trans-2-(2-fluorophenyl)ethenyl]isoquinoline oxalate




In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (563 mg, yield; 71%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (542 mg) and 2-fluorostyrene (415 mg).

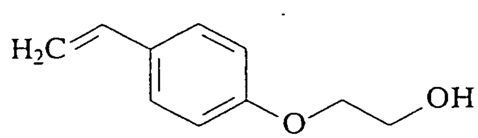
Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.24(3H,t,J=7.2Hz), 3.09(2H,q,J=7.2Hz), 3.25-3.40(4H,m), 3.50-3.70(4H,m), 7.22-7.28(2H,m), 7.31-7.38(1H,m), 7.42(1H,d,J=15.6Hz), 7.53(1H,s), 7.58(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.71(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.81(1H,d,J=15.6Hz), 7.82-7.87(1H,m), 7.90(1H,dd,J=8Hz,1.2Hz), 8.08(1H,dd,J=8Hz,1.2Hz).

FAB-Mass; 362($MH^+$).

Example 198 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline oxalate

(198-1) 2-(4-Vinylphenoxy)ethanol

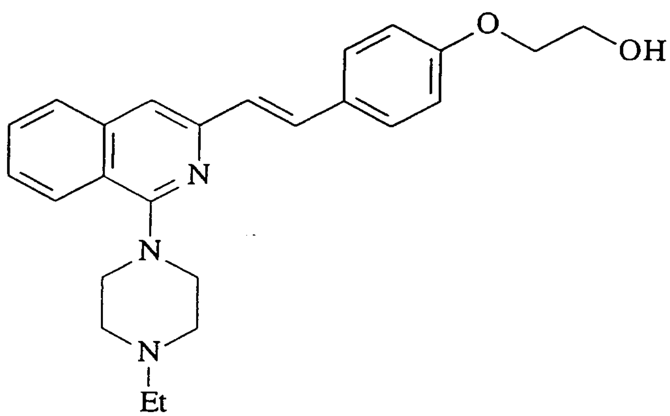


4-Hydroxybenzaldehyde (3.664 g) was dissolved in N, N-dimethylformamide (60 ml), followed by the addition of 60% sodium hydride (1.44 g) under ice-cooling. The resulting mixture was stirred at room temperature for 40 min. To the mixture was added (2-bromoethoxy)-t-butyldimethylsilane (8.612 g), and the resulting mixture was stirred at 100°C for 30 min. After the mixture was cooled as it was, it was partitioned between ethyl acetate and water. The resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was dissolved in N,N-dimethylformamide (70 ml), followed by the addition of (ethyl)triphenylphosphonium bromide (13.218 g) and 60% sodium hydride (1.623 g) under ice-cooling, and the resulting mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, extracted with hexane extraction, and then the resulting organic layer was evaporated. The resulting residue was dissolved in tetrahydrofuran (50 ml), followed by the addition of 2N hydrochloric acid (20 ml) and stirring for 1 hr. The reaction mixture was extracted with ethyl acetate, and the resulting organic layer was washed with water, dried (over $MgSO_4$) and evaporated. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system), to give the title compound as a colorless solid (3.025 g, yield; 60%).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.09(1H,s), 3.97(2H,t,J=4.6Hz), 4.09(2H,t,J=4.6Hz), 5.14(1H,dd,J=10.8Hz,0.8Hz),

5.62(1H,dd,J=17.6Hz,0.8Hz), 6.68(1H,dd,J=17.6Hz,10.8Hz), 6.83(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 6.97(1H,dd,J=2.4Hz,1.6Hz), 7.03(1H,ddd,J=8Hz,1.6Hz,0.8Hz), 7.25(1H,t,J=8Hz).

(198-2) 1-(1-Ethylpiperazin-4-yl)-3-[(E)-4-(2-hydroxyethoxy)styryl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title compound was obtained as a yellow amorphous (788 mg, yield; 89%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (580 mg) and 2-(4-vinylphenoxy)ethanol (534 mg).

Oxalate:

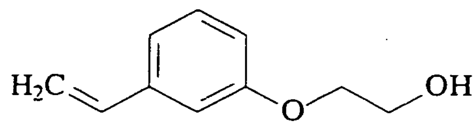
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 3.13(2H,q,J=7.2Hz), 3.30-3.42(4H,m), 3.54-3.72(4H,m), 3.71(2H,t,J=5Hz), 4.01(2H,t,J=5Hz), 6.96(2H,d,J=8.8Hz), 7.18(1H,d,J=15.6Hz), 7.42(1H,s), 7.54(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.57(2H,d,J=8.8Hz), 7.62(1H,d,J=15.6Hz), 7.68(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.85(1H,d,J=8Hz), 8.06(1H,d,J=8Hz).

FAB-Mass; 404($MH^+$).

Example 199 Synthesis of 1-(1-ethylpiperazin-4-yl)-3-

{trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl}isoquinoline oxalate

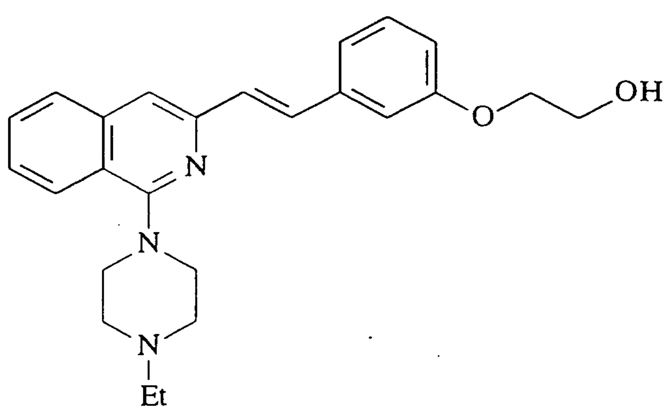
(199-1) 2-(3-Vinylphenoxy)ethanol



In the same manner as in Example 198-1, the title compound was obtained as a colorless oil (2.931 g, yield; 60%) from 3-hydroxybenzaldehyde (3.664 g), (2-bromoethoxy)-t-butyldimethylsilane (8.612 g) and (ethyl)triphenylphosphonium bromide (13.240 g).

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 2.00-2.03(1H,m), 3.95-4.00(2H,m), 4.11(2H,t,J=4.6Hz), 5.26(1H,dd,J=10.8Hz,0.8Hz), 5.74(1H,dd,J=17.6Hz,0.8Hz), 6.68(1H,dd,J=17.6Hz,10.8Hz), 6.83(1H,ddd,J=8Hz,2.4Hz,0.8Hz), 6.97(1H,dd,J=2.4Hz,1.6Hz), 7.03(1H,ddd,J=8Hz,1.6Hz,0.8Hz), 7.25(1H,t,J=8Hz).

(199-2) 1-(1-Ethylpiperazin-4-yl)-3-[trans-2-[3-(2-hydroxyethoxy)phenyl]ethenyl]isoquinoline oxalate



In the same manner as in Example 189, the oxalate of the title

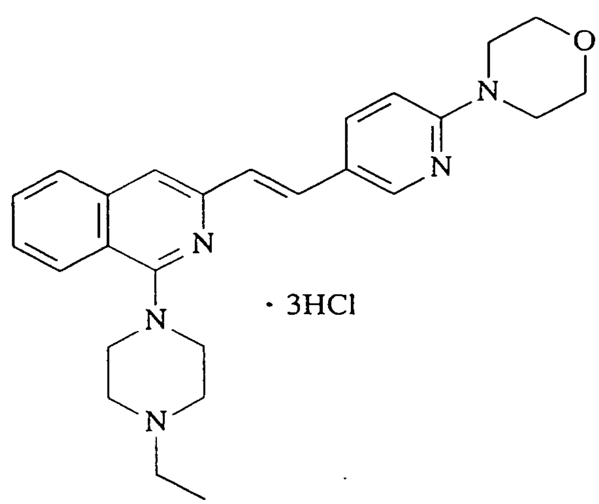
compound was obtained as a yellow amorphous (571 mg, yield; 71%) from 1-(1-ethylpiperazin-4-yl)-3-bromoisoquinoline (560 mg) and 2-(3-vinylphenoxy)ethanol (504 mg).

Oxalate:

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.25(3H,t,J=7.2Hz), 3.15(2H,q,J=7.2Hz), 3.32-3.44(4H,m), 3.52-3.74(4H,m), 3.73(2H,t,J=5Hz), 4.04(2H,t,J=5Hz), 6.87(1H,dd,J=8Hz,2.4Hz), 7.20(1H,d,J=7.6Hz), 7.22(1H,d,J=2.4Hz), 7.29(1H,dd,J=8Hz,7.6Hz), 7.35(1H,d,J=15.6Hz), 7.48(1H,s), 7.56(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.64(1H,d,J=15.6Hz), 7.70(1H,ddd,J=8Hz,7Hz,1.2Hz), 7.87(1H,d,J=8Hz), 8.07(1H,d,J=8Hz).

FAB-Mass; 404($MH^+$).

Example 200 Synthesis of 3-{(E)-2-[2-(4-morpholinyl)pyridin-5-yl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (1.06 g, yield; 95%) from

2-(4-morpholinyl)-5-vinylpyridine (1.0 g) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (832 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 190-194°C

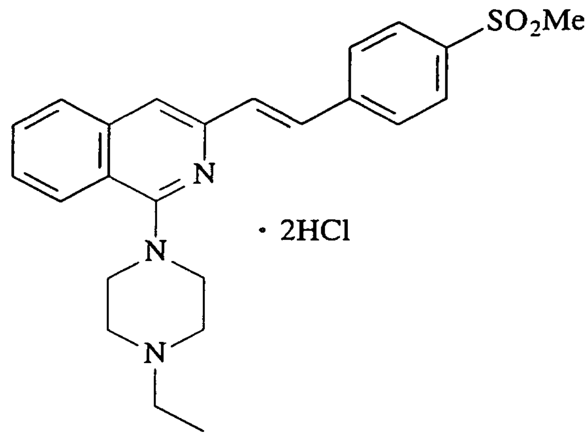
$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.35(t,J=7.2Hz,3H), 3.18-3.26(m,2H), 3.30-3.39(m,2H), 3.52-3.62(m,4H), 3.78(br,8H), 3.99(d,J=13.2Hz,2H), 7.44(d,J=16.0Hz,1H), 7.46(d,J=9.6Hz,1H), 7.49(s,1H), 7.60(t,J=8.0Hz,1H), 7.68(d,J=16.0Hz,1H), 7.73(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.09(d,J=8.0Hz,1H), 8.28(d,J=2.0Hz,1H), 8.47(d,J=9.6Hz,1H).

MS(FAB) m/z 422$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.56(q,J=7.2Hz,2H), 2.76(br,4H), 3.56(t,J=4.8Hz,8H), 3.84(t,J=4.8Hz,4H), 6.66(d,J=8.8Hz,1H), 7.02(d,J=15.6Hz,1H), 7.16(s,1H), 7.42(ddd,J=8.4,8.0,1.2Hz,1H), 7.55(ddd,J=8.4,8.0,1.2Hz,1H), 7.67(d,J=8.0Hz,1H), 7.68(d,J=15.6Hz,1H), 7.80(dd,J=8.8,2.4Hz,1H), 8.04(d,J=8.4Hz,1H), 8.37(d,J=2.4Hz,1H).

Example 201 Synthesis of 3-[(E)-2-(4-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (646 mg, yield; 70%) from 4-methylsulfonylvinylbenzene (638 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (700 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 170-174°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.34(t,J=7.2Hz,3H), 3.17-3.25(m,2H), 3.25(s,3H), 3.32-3.39(m,2H), 3.50-3.57(m,2H), 3.63(d,J=11.6Hz,2H), 4.01(d,J=13.6Hz,2H), 7.59(d,J=15.6Hz,1H), 7.60(s,1H), 7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.77(d,J=15.6Hz,1H), 7.94(br,4H), 7.95(d,J=8.0Hz,1H), 8.11(d,J=8.0Hz,1H).

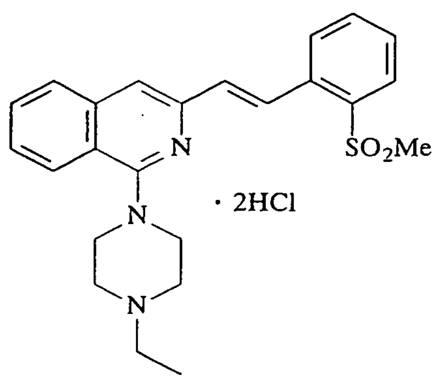
MS(FAB) m/z 422(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.57(q,J=7.2Hz,2H), 2.77(br,4H), 3.08(s,3H), 3.58(br,4H),

7.25(s,1H), 7.30(d,J=15.6Hz,1H), 7.48(ddd,J=8.4,8.0,1.2Hz,1H), 7.59(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(d,J=8.0Hz,1H), 7.75(d,J=8.4Hz,2H), 7.81(d,J=15.6Hz,1H), 7.93(d,J=8.4Hz,2H), 8.07(d,J=8.4Hz,1H).

Example 202 Synthesis of 3-[(E)-2-(2-methylsulfonylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline hydrochloride



In the same manner as in Example 189, the free compound of the title compound was obtained (599 mg, yield; 84%) from 2-methylsulfonylvinylbenzene (500 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (549 mg). The resulting free compound was converted into a hydrochloride in a conventional manner, to give the hydrochloride of the title compound as yellow crystals.

Hydrochloride:

m.p.; 146-149°C

$^1$H-NMR(400MHz,DMSO-$d_6$); $\delta$ (ppm) 1.33(t,J=7.2Hz,3H), 3.18-3.25(m,2H), 3.30(s,3H), 3.33-3.45(m,2H), 3.58-3.67(m,4H), 4.02-4.07(m,2H), 7.50(d,J=15.6Hz,1H), 7.56(s,1H), 7.58(dd,J=8.0,1.2Hz,1H), 7.60(t,J=8.0Hz,1H),

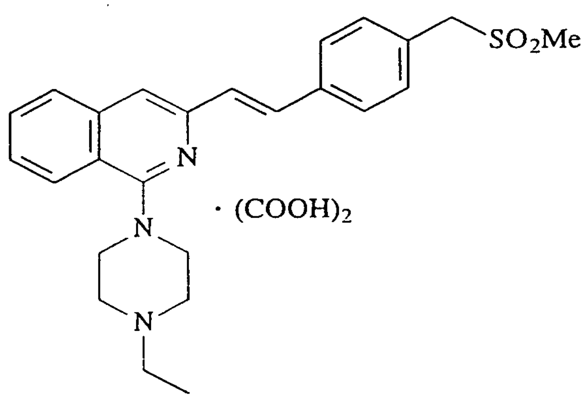
7.62(t,J=8.0Hz,1H), 7.75(t,J=8.0Hz,1H), 7.79(t,J=8.0Hz,1H), 7.95(d,J=8.0Hz,1H), 8.00(dd,J=8.0,1.2Hz,1H), 8.11(d,J=8.0Hz,1H), 8.66(d,J=15.6Hz,1H).

MS(FAB) m/z 422$(M+H)^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.18(t,J=7.2Hz,3H), 2.55(q,J=7.2Hz,2H), 2.56(br,4H), 3.15(s,3H), 3.63(br,4H), 7.19(d,J=15.6Hz,1H), 7.26(s,1H), 7.43-7.57(m,2H), 7.60(ddd,J=8.4,8.0,1.2Hz,1H), 7.64(ddd,J=8.4,8.0,1.2Hz,1H), 7.74(d,J=8.0Hz,1H), 7.87(d,J=7.2Hz,1H), 8.06(d,J=8.4Hz,1H), 8.12(d,J=8.0,1.2Hz,1H), 8.74(d,J=15.6Hz,1H).

Example 203 Synthesis of 3-[(E)-2-(4-methylsulfonylmethylphenyl)ethenyl]-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate




In the same manner as in Example 189, the free compound of the title compound was obtained (496 mg, yield; 78%) from 4-methylsulfonylmethylstyrene (432 mg) and 3-bromo-1-(4-ethylpiperazin-1-yl)isoquinoline (470 mg). The resulting free compound was converted into an oxalate in a conventional

manner, to give the oxalate of the title compound as yellow crystals.

Oxalate:

m.p.; 245-247°C

$^1$H-NMR(400MHz,DMSO-$d_3$); $\delta$ (ppm) 1.28(t,J=7.2Hz,3H), 2.93(s,3H), 3.18(q,J=7.2Hz,2H), 3.42(br,4H), 3.67(br,4H), 4.52(s,2H), 7.40(d,J=15.6Hz,1H), 7.44(d,J=8.4Hz,2H), 7.52(s,1H), 7.59(t,J=8.0Hz,1H), 7.70(d,J=8.4Hz,2H), 7.71(d,J=15.6Hz,1H), 7.72(t,J=8.0Hz,1H), 7.91(d,J=8.0Hz,1H), 8.10(d,J=8.0Hz,1H).

MS(FAB) m/z 436(M+H)$^+$.

Free compound:

$^1$H-NMR(400MHz,$CDCl_3$); $\delta$ (ppm) 1.19(t,J=7.2Hz,3H), 2.58(q,J=7.2Hz,2H), 2.78(br,7H), 3.58(br,4H), 4.27(s,2H), 7.20(d,J=15.6Hz,1H), 7.22(s,1H), 7.41(d,J=8.4Hz,2H), 7.45(ddd,J=8.4,8.0,1.2Hz,1H), 7.58(ddd,J=8.4,8.0,1.2Hz,1H), 7.63(d,J=8.4Hz,2H), 7.72(d,J=8.0Hz,1H), 7.78(d,J=15.6Hz,1H), 8.06(d,J=8.4Hz,1H).

Example 204 Synthesis of 3-{(E)-2-[3-(4-morpholinyl)phenyl]ethenyl}-1-(4-ethylpiperazin-1-yl)isoquinoline oxalate